Cordis Checkmate™ Catheter

Instructions for Use

Caution: Federal Law restricts this device to sale by or on the order of a physician.

Table of Contents

1. Device Description

The Cordis Checkmate Catheter is a component of the Cordis Checkmate System; the other component of the Cordis Checkmate System is the Cordis Checkmate Delivery System (see also Section 12.1). The Cordis Checkmate Catheter (this package) includes:

1. A Radiation Delivery Catheter (Checkmate Catheter)
   - A single lumen catheter with a distal rapid exchange tip which serves as a conduit for the non-radioactive dummy ribbon and the radioactive Ir-192 source ribbon. The catheter contains a single, closed ended source lumen that is isolated from patient and blood contact. The source lumen is accessed through a single port hub.
   - A single radiopaque marker identifies the distal end of the source lumen and is located slightly proximal to the guidewire port.
   - A guidewire (not included) exits the catheter at the port, approximately 4 mm from the distal tip of the catheter.
   - The catheter has two (2) exit markers (optional) along the proximal shaft that indicate, approximately, the exit of the distal tip of the Checkmate Catheter from the guiding catheter (brachial at 90 cm and femoral at 100 cm from the distal tip).
   - An additional (optional) marker indicates the transition from a smaller catheter shaft diameter (distal) to a larger shaft diameter (proximal).

2. A Non-Radioactive Dummy Ribbon
   - Provides reinforcement of the Checkmate Catheter during shipment and upon introduction into the vascular system and is used to position the Checkmate Catheter across the target lesion prior to use of a radioactive source ribbon.
   - This yellow ribbon contains a strand of non-radioactive seeds divided and/or bracketed by radiopaque markers that match the length and configuration of the radioactive zone of the source ribbon.

3. A Source Lumen Plug
   - Prevents movement of the non-radioactive dummy ribbon during Checkmate Catheter insertion and manipulation and is removable.

2. Indications

The Cordis Checkmate Catheter is intended for the delivery of therapeutic doses of gamma radiation for the purpose of reducing in-stent restenosis. The system is for use in the treatment of native coronary arteries with in-stent restenosis following percutaneous revascularization using current interventional techniques.

- This system is for use in vessels 2.75 – 4.0 mm in diameter and for lesions up to and including 45 mm in length.

3. Contra-indications

Intracoronary radiation therapy is generally contraindicated in the following patient types:

- Patients in whom antiplatelet and/or anticoagulant therapy is contraindicated.

4. Warnings

[redacted]

The Cordis Checkmate System should not be used for indexing procedures as it may result in overexposure of overlapping treatment areas.

5. Precautions

See also Section 12, "Operator Manual".

- The Cordis Checkmate Catheter should only be used in combination with the Cordis Checkmate Delivery System.
- Only physicians who have received adequate training should perform intravascular brachytherapy.
- Intravascular brachytherapy should only be performed at hospitals with the appropriate licensing from the governing nuclear regulatory agency for use of radiation for intravascular therapeutic purposes.
- Intravascular brachytherapy should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Do not expose the product to solvents (e.g. alcohol, hydrogen peroxide).
- Follow the site specific radiation safety procedures.

6. Special Considerations

Safety and effectiveness has not been demonstrated in the following populations:

- Patient with previous intravascular brachytherapy of the same vessel segment or previous radiation treatment in the immediate vicinity.
- Patients who are pregnant.
- Patients with known genetic radiation sensitivity disorders (e.g. ataxia-telangiectasia, etc.)
- Patients with saphenous vein graft disease.

7. Adverse Events

7.1 Observed Adverse Events

A total of 252 patients were enrolled in a single multi-center randomized clinical trial (GAMMA-I trial) to evaluate the use of the Cordis Checkmate System for treatment of in-stent restenosis. These patients form the basis for the reported observed events (see Clinical Studies).

Additionally, data is provided on the SCRIPPS-I trial (single center, randomized trial, 60 patients) and the WRIST trial (single center, randomized trial, 130 patients). Both studies used the Ir-192 Source Ribbon for treatment of in-stent restenosis.

Table 7.1 Major Adverse Cardiac Events (to 270 days)
All patients in GAMMA-I Trial (N=252)

	Radiation (N=131)	Placebo (N=121)	Relative Risk [95% CI]	Difference [95% CI]
Any MACE (Death, MI, Em. CABG, TLR)	28.2% (37/131)	43.8% (53/121)	0.64 [0.46, 0.90]	-15.6% [-27.3%, -3.8%]
Death	3.1% (4/131)	0.8% (1/121)	3.69 [0.49, 28.03]	2.2% [-1.1%, 5.6%]
Myocardial Infarction (Q or Non-Q)	12.2% (16/131)	6.6% (8/121)	1.85 [0.83, 4.10]	5.6% [-1.5%, 12.7%]
Q Wave MI	5.3% (7/131)	3.3% (4/121)	1.62 [0.49, 5.33]	2.0% [-3.0%, 7.0%]
Non-Q Wave MI	6.9% (9/131)	3.3% (4/121)	2.08 [0.68, 6.40]	3.6% [-1.8%, 8.9%]
Emergent CABG	0.0% (0/131)	0.0% (0/121)	- [-,-]	0.0% [0.0%, 0.0%]
Target Lesion Revascularization	24.4% (32/131)	42.1% (51/121)	0.58 [0.41, 0.83]	-17.7% [-29.2%, -6.3%]
TL-CABG	9.9% (13/131)	20.7% (25/121)	0.48 [0.26, 0.88]	-10.7% [-19.6%, -1.9%]
TL-PTCA	19.8% (26/131)	27.3% (33/121)	0.73 [0.46, 1.14]	-7.4% [-17.9%, 3.0%]
Perforation	0.8% (1/131)	0.0% (0/121)	- [-,-]	0.8% [-0.7%, 2.3%]
Bleeding Complications	2.3% (3/131)	0.8% (1/121)	2.77 [0.32, 23.91]	1.5% [-1.6%, 4.5%]
Vascular Complications	3.1% (4/131)	1.7% (2/121)	1.85 [0.35, 9.66]	1.4% [-2.3%, 5.1%]
Hematological Dyscrasia	0.8% (1/131)	1.7% (2/121)	0.46 [0.04, 4.76]	-0.9% [-3.6%, 1.8%]
CVA	0.8% (1/131)	2.5% (3/121)	0.31 [0.04, 2.58]	-1.7% [-4.9%, 1.4%]
Acute Stent Thrombosis (to 30 days)	0.8% (1/131)	1.7% (2/121)	0.46 [0.04, 4.76]	-0.9% [-3.6%, 1.8%]
Late Thrombosis	5.3% (7/131)	0.8% (1/121)	6.47 [0.81, 51.79]	4.5% [0.3%, 8.7%]
Late Total Occlusion	12.6% (14/111)	5.8% (6/103)	2.17 [0.87, 5.42]	6.8% [-0.8%, 14.4%]

Numbers are % (counts/sample size) or Mean ± SD. CI = Confidence Interval
Relative Risk = Radiation/Placebo SE = sqrt $\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}$ CI = RR*exp(±1.96*SE)
Difference = Radiation – Placebo SE = sqrt $(p_1*q_1/n_1+p_2*q_2/n_2)$ CI = Diff±1.96*SE

As shown in Table 7.1, 5 patients died during the GAMMA-I trial. The 5 deaths occurred between 0 and 264 days post radiation and were due to: cardiac tamponade (n=1), hemorrhage following by-pass surgery (n=1), sudden cardiac death (n=2) and suicide (n=1). There were no device delivery failures and there were 11 cases of stent thrombosis, 3 acute stent thrombosis and 8 late thrombosis.

Table 7.2 Major Adverse Cardiac Events (to 180 days)
All patients in SCRIPPS-I Trial (N=60)

	Radiation (N=29)	Placebo (N=31)	Relative Risk [95% CI]	Difference [95% CI]
Any MACE (Death, MI, Em. CABG, TLR)	20.7% (6/29)	22.6% (7/31)	0.92 [0.35, 2.42]	-1.9% [-22.7%, 18.9%]
Death	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Myocardial Infarction (Q or Non-Q)	6.9% (2/29)	3.2% (1/31)	2.14 [0.21, 21.40]	3.7% [-7.5%, 14.8%]
Q Wave MI	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Non-Q Wave MI	6.9% (2/29)	3.2% (1/31)	2.14 [0.21, 21.40]	3.7% [-7.5%, 14.8%]
Emergent CABG	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Target Lesion Revascularization	17.2% (5/29)	22.6% (7/31)	0.76 [0.27, 2.14]	-5.3% [-25.5%, 14.8%]
TL-CABG	3.4% (1/29)	3.2% (1/31)	1.07 [0.07, 16.68]	0.2% [-8.9%, 9.3%]
TL-PTCA	13.8% (4/29)	19.4% (6/31)	0.71 [0.22, 2.27]	-5.6% [-24.3%, 13.2%]
Perforation	0.0% (0/29)	0.0% (0/31)	-[-, -]	0.0% [-,-]
Bleeding Complications	0.0% (0/29)	6.5% (2/31)	0.00 [-,-]	-6.5% [-15.1%, 2.2%]
Vascular Complications	0.0% (0/29)	0.0% (0/31)	- [-,-]	0.0% [-,-]
CVA	0.0% (0/29)	3.2% (1/31)	0.00 [-,-]	-3.2% [-9.4%, 3.0%]
Acute Stent Thrombosis (to 30 days)	3.4% (1/29)	0.0% (0/31)	- [-,-]	3.4% [-3.2%, 10.1%]
Late Thrombosis	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Late Total Occlusion	3.6% (1/28)	0.0% (0/28)	-[-,-]	3.6% [-3.3%, 10.5%]

Numbers are % (counts/sample size) or Mean ± SD. CI = Confidence Interval
Relative Risk = Radiation/Placebo SE = sqrt $\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}$ CI = RR*exp(±1.96*SE)
Difference = Radiation – Placebo SE = sqrt $(p_1*q_1/n_1+p_2*q_2/n_2)$ CI = Diff±1.96*SE
Late total occlusions were those occlusions in a patient who had angiographic documentation of 100% stenosis at the target site 31 days or more after the index procedure.

As shown in Table 7.2, there were no deaths in the SCRIPPS-I trial. There were no device delivery failures and there was 1 acute stent thrombosis.

Table 7.3 Major Adverse Cardiac Events (to 180 days +/- 30 days)
All patients in WRIST Trial (N=130)

	Radiation (N=65)	Placebo (N=65)	Relative Risk [95% CI]	Difference [95% CI]
Any MACE (Death, MI, Em. CABG, TLR)	29.2% (19/65)	67.7% (44/65)	0.43 [0.29, 0.65]	-38.5% [-54.6%, -22.3%]
Death	4.6% (3/65)	6.2% (4*/65)	0.75 [0.18, 3.22]	-1.5% [-9.4%, 6.4%]
Myocardial Infarction (Q or Non-Q)				
Q Wave MI	0.0% (0/65)	0.0% (0/65)	- [-,-]	0.0% [-,-]
Non-Q Wave MI	16.9% (11/65)	12.3% (8/65)	1.38 [0.59,3.20]	4.6% [-7.7%, 16.9%]
Target Lesion Revascularization	15.4% (10/65)	63.1% (41/65)	0.24 [0.13, 0.44]	-47.7% [-62.6%, -132.8%]
CABG	7.7% (5/65)	6.2% (4/65)	1.25 [0.35, 4.45]	-1.5% [-7.3%, 10.4%]
PTCA	9.2% (6/65)	61.5% (40/65)	0.15 [0.07, 0.33]	-52.3% [-66.3%, -38.3%]
Vascular Complications	12.3% (8/65)	12.3% (8/65)	1.00 [0.40, 2.50]	0.0% [-11.5%, 11.5%]
TVR (not involving target lesion)	12.3% (8/65)	4.6% (3/65)	2.67 [0.74, 9.61]	7.7% [-1.9%, 17.3%]
CVA	0.0% (0/65)	0.0% (0/65)	- [-,-]	0.0% [-,-]
Subacute Closure (to 30 days)	0.0% (0/65)	0.0% (0/65)	- [-,-]	0.0% [-,-]
Late Thrombosis**	3.1% (2/65)	0.0% (0/65)	- [-,-]	3.1% [-1.1%, 7.3%]
Late Total Occlusion**	13.8% (9/65)	1.5% (1/65)	9.00 [1.17, 69.02]	12.3% [3.4%, 21.2%]

Numbers are % (counts/sample size) or Mean $\pm$ SD. CI = Confidence Interval
Relative Risk = Radiation/Placebo SE = sqrt $\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}$ CI = RR*exp($\pm$1.96*SE)
Difference = Radiation – Placebo SE = sqrt $(p_1*q_1/n_1+p_2*q_2/n_2)$ CI = Diff$\pm$1.96*SE
* One patient died on day 212 and one on day 214.
** Additionally, the rates of late thrombosis and late total occlusion for the crossover group are 5.1% (2/39) and 12.8% (5/39), respectively.

As shown in Table 7.3, 7 patients died during the WRIST trial. The 7 deaths occurred between 0 and 214 days post radiation, all were cardiac deaths. There were no device delivery failures and there were 2 cases of late thrombosis.

7.2 Potential Adverse Events

Adverse events (in alphabetical order) which may be associated with intracoronary radiation treatment (including those listed in Table 7.1).

- Acute myocardial infarction
- Allergic reaction
- Aneurysm
- Arrhythmias, including VF and VT
- Death
- Dissection
- Drug reactions to antiplatelet agents/contrast medium
- Embolization
- Emergent Coronary Artery Bypass Surgery
- Hematological dyscrasia
- Hemorrhage, requiring transfusion
- Hypotension/Hypertension
- Infection and/or pain at the access site
- Ischemia, myocardial
- Malignant or pre-malignant transformation
- Perforation
- Pseudoaneurysm
- Restenosis of the radiated segment
- Spasm, coronary artery
- Stent embolization
- Stent thrombus/occlusion (acute, late)
- Stroke/cerebrovascular accident
- Total occlusion of coronary artery
- Vascular complications (e.g. fibrosis, necrosis, intimal proliferation)

For adverse events associated with antiplatelet and/or anticoagulant therapy, refer to the manufacturer's Instructions for Use.

8. Clinical Studies

GAMMA-I Trial (Pivotal Study)

This was a multi-center, prospective, randomized, double-blind trial designed to evaluate the safety and effectiveness of localized radiation therapy following percutaneous revascularization using current interventional techniques in patients with in-stent restenosis. A total of 252 patients were treated at 12 US investigational centers.

Primary Endpoint: The primary endpoint for the GAMMA-I trial was a composite of major adverse cardiac events including death, Q-wave and non-Q-wave myocardial infarction (MI), emergent CABG and target lesion revascularization (TLR) at 9 months post-procedure. **TLR was defined** as any clinically driven revascularization of the target lesion using either bypass surgery or percutaneous (i.e. angioplasty) techniques. An independent Clinical Events Committee, blinded to treatment assignment, adjudicated all major clinical endpoints for the GAMMA-I trial.

Patients Studied: Patients with in-stent restenosis of native coronary arteries, 2.75 – 4.0 mm in diameter and $\leq$ 45 mm in length, treated with current interventional techniques were admitted to the GAMMA-I trial.

Methods: Patients with in-stent restenosis underwent redilatation of the restenosis using current interventional techniques including high pressure (> 12 atmospheres) balloon inflation with a balloon-to-artery ratio of 1-1.2:1. If by angiography or ultrasound, a <30% residual stenosis was not obtained after this vigorous dilatation, or if a significant dissection was created inside the stent or the stent border, or if the restenotic lesion was at the stent border, another one or two approved non-coil stents were implanted as needed within and/or overlapping the original stent to cover the restenotic segments. New stents were optimally dilated using routine techniques.

Immediately after successful coronary intervention, the Cordis Checkmate Catheter and dummy ribbon were introduced over the indwelling guidewire, using the catheter's rapid exchange tip. After the Checkmate Catheter was positioned across the target lesion, the patient was randomized to treatment with either a placebo ribbon or Iridium-192 source ribbon. The dwell time for each individual patient was calculated based on the vessel diameter (as determined by intravascular ultrasound measurement), the number of seeds of the treatment ribbon and the activity of the treatment ribbon on the day of the procedure. This information is used by a radiation oncologist and physicist to determine the time required to deliver 800 cGy to the target farthest from the radiation source, with no more that 3000 cGy delivered to the target closet to the source.

Clinical Follow-up was completed at one, six and nine months; all patients underwent angiographic follow-up at 6 months. Baseline QCA was performed pre- and post-procedure. The baseline characteristics of the two patient populations in the GAMMA-I trial were similar. All treated patients were included in the intent-to-treat analysis. Antiplatelet therapy included aspirin 325 mg/daily (indefinitely) and ticlopidine 250 mg b.i.d for 8 weeks if a stent was implanted at the target lesion during the study procedure.

Results: In suitable patients with restenotic coronary lesions, an interventional procedure (IP) followed by intravascular brachytherapy (Radiation) resulted in a statistically significant improvement in late angiographic and intravascular ultrasound (IVUS) results, a lower six-month angiographic restenosis rate, and lower major adverse cardiac events (MACE) at 9 months when compared to IP and Placebo intravascular brachytherapy. The rate of late stent thrombosis was higher in the Radiation arm.

Clinical Trials Comparison

	GAMMA-I	SCRIPPS-I	WRIST	SCRIPPS-III	WRIST Plus
Trial	Pivotal Trial Multi center, prospective, randomized	Supportive Trial Single center, prospective, randomized	Supportive Trial Single center, prospective, randomized	Supportive Trial Multi center, registry	Supportive Trial Single center, registry
Total # of Patients Enrolled	252	60	130	500	120
Patients Studied	Native coronary arteries 2.75 - 4.0 mm diameter ≤ 45 mm length	Native coronary arteries and SVG's 3.0 – 5.5 mm diameter <30 mm length	Native coronary arteries and SVG's 3.0 – 5.0 mm diameter < 50 mm length	Native coronary arteries and SVG's 2.75 – 4.0 mm diameter < 81 mm length	Native coronary arteries and SVG's 2.5 – 5.0 mm diameter < 80 mm length
Devices Used	6, 10 or 14 seed ribbons 4F Catheter	5 or 9 seed ribbon 4F Catheter	5, 9 or 13 seed ribbon 5F Catheter	6 – 22 seed ribbons 4F Catheter	6-23 seed ribbons 4F or 5F Catheter
Methods	Outlined on previous page	Similar to GAMMA-1	Similar to GAMMA-I	Similar to GAMMA-I	Similar to GAMMA-I
Dosimetry	IVUS based 800-3000 cGy	IVUS based 800-3000 cGy	No IVUS 1500 cGy at 2 mm from the center of the source	No IVUS 1400 cGy at 2 mm	No IVUS 1400 cGy or 1500 cGy at 2 mm from the center of the source
Antiplatelet Therapy	8-weeks if new stent was placed	2 weeks if new stent was placed	4 weeks (all patients)	6 months if no new stent 12 months if new stent is placed	6 months (all patients)
Follow-up	6 months angiographic 1 & 9 months clinic 2, 24, 36 months telephone FU	6 & 36 months angiographic 12, 24, 36, 48, 60 months telephone FU	6 months angiographic 1, 6, 12 & 24 months clinic	1 & 9 months clinic 2 & 12 months telephone FU	6 & 24 months angiographic 1 & 12 months clinic

Table 8.1 GAMMA-I Principal Effectiveness and Safety Results (to 270 days)
All Patients Treated (N=252)

Effectiveness Measures	Radiation (N=131)	Placebo (N=121)	Relative Risk [95% CI]	Difference [95% CI]
Lesion Success	100.0% (131/131)	98.3% (119/121)	1.02 [0.99, 1.04]	1.7% [-0.6%, 3.9%]
Procedure Success	100.0% (131/131)	98.3% (119/121)	1.02 [0.99, 1.04]	1.7% [-0.6%, 3.9%]
Device Success	100.0% (131/131)	98.3% (119/121)	1.02 [0.99, 1.04]	1.7% [-0.6%, 3.9%]
Post Procedure In-Stent Percent Diameter Stenosis (% DS) Mean±SD (N)	8.8%±17.9% (129)	8.9%±19.0% (117)	N/A	-0.1% [-4.8%, 4.5%]
Range (min, max)	(-49.9%, 48.8%)	(-55.8%, 59.1%)		
Follow-Up In-Stent Percent Diameter Stenosis (% DS) Mean±SD(N)	33.6%±32.3% (111)	50.8%±22.0% (103)	N/A	-17.2% [-24.7%, -9.7%]
Range (min, max)	(-48.5%, 100.0%)	(-0.8%, 100.0%)		
In-Stent Late Loss (mm) Mean±SD (N)	0.73±0.79 (111)	1.14±0.65 (101)	N/A	-0.40 [-0.60, -0.20]
Range (min, max)	(-0.56, 3.37)	(-0.47, 3.30)		
6 Month In-Lesion (Stent+Probe+Edge) Binary Restenosis Rate	32.4% (36/111)	55.3% (57/103)	0.59 [0.43, 0.80]	-22.9% [-35.9%, -9.9%]
6 Month In-Stent Binary Restenosis Rate	21.6% (24/111)	50.5% (52/103)	0.43 [0.29, 0.62]	-28.9% [-41.2%, -16.5%]
Difference of Index and F/U Mean Difference of Stent and Lumen	-0.75±1.13 (35)	-1.55±1.15 (33)	N/A	0.80 [0.25, 1.35]
	(-3.80, 2.14)	(-4.48, 0.20)		
TLR-Free at 270 days*	74.8% [65.7%, 83.9%]	56.7% [46.1%, 67.3%]	1.32 [1.06, 1.65]	18.1% [4.1%, 32.1%]
TVR-Free at 270 days*	66.2% [56.3%, 76.1%]	52.5% [41.9%, 63.1%]	1.26 [0.98, 1.62]	13.8% [-0.7%, 28.2%]
TVF-Free at 270 days*	62.3% [52.1%, 72.5%]	51.6% [41.0%, 62.3%]	1.21 [0.93, 1.57]	10.7% [-4.1%, 25.4%]
MACE-Free at 270 days*	70.8% [61.2%, 80.4%]	55.0% [44.4%, 65.7%]	1.29 [1.02, 1.63]	15.8% [1.4%, 30.1%]
Safety Measures and Other Clinical Events				
In-Hospital MACE	2.3% (3/131)	3.3% (4/121)	0.69 [0.16, 3.01]	-1.0% [-5.1%, 3.1%]
Out-of-Hospital MACE to 270 days	26.7% (35/131)	42.1% (51/121)	0.63 [0.45, 0.90]	-15.4% [-27.0%, -3.8%]
Bleeding Complications to 270 days	2.3% (3/131)	0.8% (1/121)	2.77 [0.32, 23.91]	1.5% [-1.6%, 4.5%]
Vascular Complications to 270 days	3.1% (4/131)	1.7% (2/121)	1.85 [0.35, 9.66]	1.4% [-2.3%, 5.1%]
Hematologic Dyscrasia to 270 days	0.8% (1/131)	1.7% (2/121)	0.46 [0.04, 4.76]	-0.9% [-3.6%, 1.8%]
CVA to 270 days	0.8% (1/131)	2.5% (3/121)	0.31 [0.04, 2.58]	-1.7% [-4.9%, 1.4%]
Acute Stent Thrombosis	0.8% (1/131)	1.7% (2/121)	0.46 [0.04, 4.76]	-0.9% [-3.6%, 1.8%]
Late Thrombosis	5.3% (7/131)	0.8% (1/121)	6.47 [0.81, 51.79]	4.5% [0.3%, 8.7%]
Late Total Occlusion	12.6% (14/111)	5.8% (6/103)	2.17 [0.87, 5.42]	6.8% [-0.8%, 14.4%]

Numbers are % (counts/sample size) or Mean±SD — CI = Confidence Interval

Relative Risk = Radiation/Placebo — SE = sqrt $\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}$ — CI = RR* exp (± 1.96* SE)

Difference = Radiation – Placebo — SE = sqrt $(p_1*q_1/n_1+p_2*q_2/n_2)$ — CI = Diff ± 1.96* SE

N/A = Not Applicable

Lesion Success = Attainment of a <50% residual stenosis using any percutaneous method.

Procedure Success = Attainment of a <50% residual diameter stenosis using any percutaneous method and no in-hospital MACE.

Device Success = Attainment of a <50% residual stenosis and successful delivery of the radiation device.

Restenosis was defined as ≥50% in-stent diameter stenosis at the follow-up angiogram.

*Survival Estimates from Kaplan-Meier estimate. Standard Error estimates by Peto formula.

KM Relative Risk = $S_{Radiation}/S_{Placebo}$ — $SE_{RR}=sqrt\{(SE_{Radiation}/S_{Radiation})^2+(SE_{Placebo}/S_{Placebo})^2\}$ — $CI = RR*exp(\pm 1.96*SE_{RR})$

KM Difference = $S_{Radiation} - S_{Placebo}$ — $SE_{Diff} = sqrt(SE_{Radiation}^2+SE_{Placebo}^2)$ — $CI = Diff \pm 1.96*SE_{Diff}$

TLR-Free = No target lesion revascularization.

TVR-Free = No target vessel revascularization.

TVF-Free = No death, MI, or target lesion revascularization.

MACE-Free = No death, Q wave or non-Q wave MI, emergent CABG, or target lesion revascularization.

MACE = Death, Q wave or non-Q wave MI, emergent CABG, or target lesion revascularization.

In-Hospital MACE = Death, Q wave or non-Q wave MI, emergent CABG, or target lesion revascularization prior to hospital discharge.

Out-of-Hospital MACE = Death, Q wave or non-Q wave MI, emergent CABG, or target lesion revascularization after hospital discharge.

Bleeding Complications = Transfusions of blood products due to blood loss resulting from the percutaneous revascularization procedure.

Vascular Complications = Hematoma > 4 cm, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, and vascular surgical repair.

CVA = Acute neurological deficits recorded by the clinical sites that persisted > 24 hours.

Acute Stent Thrombosis = Angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven angiographic restudy for documented ischemia (chest pain or ECG changes). Any death not attributed to a non-cardiac cause within the first 30 days was considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

Late Thrombosis = Myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and in a newly implanted bypass graft at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.

Late Total Occlusion = Consists of Late Thrombosis and Total Occlusion.

Table 8.2 SCRIPPS-I Principal Effectiveness and Safety Results (to 180 days)
All Patients Treated (N=60)

Effectiveness Measures	Radiation (N=29)	Placebo (N=31)	Relative Risk [95% CI]	Difference [95% CI]
Lesion Success	100.0% (29/29)	93.5% (29/31)	1.07 [0.97, 1.18]	6.5% [-2.2%, 15.1%]
Procedure Success	100.0% (29/29)	93.5% (29/31)	1.07 [0.97, 1.18]	6.5% [-2.2%, 15.1%]
Device Success	100.0% (29/29)	90.3% (28/31)	1.11 [0.98, 1.24]	9.7% [-0.7%, 20.1%]
Post Procedure In-Stent Percent Diameter Stenosis (% DS)				
Mean±SD (N)	9.4±22.8% (29)	7.0%±23.9% (31)	N/A	2.5% [-9.6, 14.5]
Range (min, max)	(-64.1%, 38.0%)	(-36.0%, 46.4%)		
Post-Procedure In-Stent+Border % DS				
Mean±SD(N)	24.4%±9.5% (29)	18.9±18.1% (31)	N/A	5.6% [-2.0%, 13.1%]
Range (min, max)	(-0.8%, 39.8%)	(-24.3%, 53.2%)		
6 Month F/U In-Stent+Border % DS				
Mean±SD (N)	43.2%±23.5% (28)	41.8%±24.2% (28)	N/A	1.4% [-11.4%,14.2%]
Range (min, max)	(16.5%, 100%)	(-23.8%, 78.6%)		
6 Month F/U In-Stent+Border Late Loss				
Mean±SD (N)	0.66±0.91 (28)	0.78±0.94 (28)	N/A	-0.13 [-0.62, 0.37]
Range (min, max)	(-0.62, 2.73)	(-0.46, 3.49)		
6 Month In-Stent+Border Restenosis Rate	21.4% (6/28)	46.4% (13/28)	0.46 [0.21, 1.00]	-25.0% [-48.9%, -1.1%]
Difference between Post-Procedure and 6-Month F/U Mean Intimal Hyperplasia CSA (mm^2)				
Mean±SD (N)	-0.68±0.97 (18)	-2.14±1.66 (18)	N/A	1.47 [0.55, 2.39]
Range (min, max)	(-2.90, 0.70)	(-5.60, -0.40)		
TLR-Free at 180 days*	82.6% [68.5%, 96.7%]	77.4% [62.4%, 92.5%]	1.07 [0.82, 1.38]	5.2% [-15.4%, 25.8%]
TVR-Free at 180 days*	82.8% [68.7%, 96.8%]	71.0% [54.6%, 87.3%]	1.17 [0.88, 1.55]	11.8% [-9.8%, 33.3%]
TVF-Free at 180 days*	79.3% [64.2%, 94.4%]	71.0% [54.6%, 87.3%]	1.12 [0.83, 1.51]	8.3% [-13.9%, 30.6%]
MACE-Free at 180 days*	79.2% [64.1%, 94.3%]	77.4% [62.4%, 92.5%]	1.02 [0.78, 1.34]	1.7% [-19.6%, 23.1%]
Safety Measures and Other Clinical Events				
In-Hospital MACE	0.0% (0/29)	0.0% (0/31)	- [-,-]	0.0% [-,-]
Out-of-Hospital MACE to 180 days	20.7% (6/29)	22.6% (7/31)	0.92 [0.35, 2.42]	-1.9% [-22.7%, 18.9%]
Bleeding Complications to 180 days	0.0% (0/29)	6.5% (2/31)	0.00 [-,-]	-6.5 [-15.1%, 2.2%]
Vascular Complications to 180 days	0.0% (0/29)	0.0% (0/31)	- [-,-]	0.0% [-,-]
CVA to 180 days	0.0% (0/29)	3.2% (1/31)	1.00 [-, -]	-3.2% [-9.4%, 3.0%]
Acute Stent Thrombosis (to 30 days)	3.4% (1/29)	0.0% (0/31)	- [-,-]	3.4% [-3.2%, 10.1%]
Late Thrombosis	0.0% (0/29)	0.0% (0/31)	- [-,-]	0.0% [-,-]
Late Total Occlusion	3.6% (1/28)	0.0% (0/28)	- [-,-]	3.6% [-3.3%, 10.5%]

Numbers are % (counts/sample size) or Mean ± SD — CI = Confidence Interval

Relative Risk = Radiation/Placebo — SE = sqrt $\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}$ — CI = RR* exp (± 1.96* SE)

Difference = Radiation – Placebo — SE = sqrt $(p_1*q_1/n_1+p_2*q_2/n_2)$ — CI = Diff ± 1.96* SE

N/A = Not applicable.

Device Success = The attainment of a <50% residual stenosis and successful delivery of the radiation device.

Lesion Success = The attainment of a <50% residual stenosis using any percutaneous method.

Procedure Success = The attainment of a <50% residual stenosis using any percutaneous method and no in-hospital MACE.

In-Hospital MACE = Death, Q wave or non-Q wave MI, target lesion revascularization, and emergent CABG prior to hospital discharge.

Out-of-Hospital MACE = Death, Q wave or non-Q wave MI, target lesion revascularization, and emergent CABG after hospital discharge.

*Survival Estimates from Kaplan-Meier estimates. Standard Error estimates from Peto formula.

KM Relative Risk = $S_{Radiation}/S_{Placebo}$ — $SE_{RR}=sqrt\{(SE_{Radiation}/S_{Radiation})^2+(SE_{Placebo}/S_{Placebo})^2\}$ — $CI = RR*exp(\pm 1.96*SE_{RR})$

KM Difference = $S_{Radiation} - S_{Placebo}$ — $SE_{Diff} = sqrt\{SE_{Radiation}^2+SE_{Placebo}^2\}$ — $CI = Diff \pm 1.96*SE_{Diff}$

TLR-Free = No target lesion revascularization.

TVR-Free = No target vessel revascularization.

TVF-Free = No death, Q wave or non-Q wave MI, or target vessel revascularization.

MACE-Free = No death, Q wave or non-Q wave MI, target lesion revascularization, or emergent CABG.

Bleeding Complications = Bleeding complications were defined as transfusions of blood products due to blood loss resulting from the percutaneous revascularization procedure.

Vascular Complications = Hematoma > 4 cm, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, and Vascular surgical repair.

CVA = Cerebrovascular accident was defined as acute neurological deficits recorded by the clinical sites that persisted > 24 hours.

Acute Stent Thrombosis = Angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven angiographic restudy for documented ischemia (chest pain or ECG changes). Any death not attributed to a non-cardiac cause within the first 30 days was considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

Late Total Occlusion = Consists of Late Thrombosis and Total Occlusion.

Table 8.3 WRIST Principal Effectiveness and Safety Results (to 180 days +/- 30 days) All Patients Treated (N=130)

Effectiveness Measures	Radiation (65=Patients, 65=Lesions)	Placebo (65=Patients, 65=Lesions)	Relative Risk (95% CI)	Difference (95% CI)
Lesion Success	100% (64/64)	98.4% (63/64)	1.02 (0.99, 1.05)	1.6 (-1.5, 4.7)
Device Success	100% (64/64)	96.9% (62/64)	1.03 (0.99, 1.08)	3.1 (-1.2, 7.5)
Procedure Success	100% (64/64)	98.4% (63/64)	1.02 (0.99, 1.05)	1.6 (-1.5, 4.7]
Post-Procedure In-Lesion Percent Diameter Stenosis				
(% DS) Mean±SD (N)	28.32±11.93 (64)	27.30±11.99 (64)	N/A	1.02 (-3.16, 5.20)
Range (min, max)	(-10.07, 63.21)	(2.29, 55.88)		
Post Procedure In-Stent Percent Diameter Stenosis				
(% DS) Means±SD (N)	19.77±15.16 (64)	20.45±14.75 (64)	N/A	-0.68 (-5.91, 4.56)
Range (min, max)	(-18.80, 43.01)	(-20.23, 50.46)		
Late Loss In-Stent (QCA)				
Mean±SD (N)	0.24±0.84 (59)	0.96±-0.68 (55)	N/A	-0.72 (-1.01, -0.44)
Range (min, max)	(-1.20, 2.95)	(-0.82, 2.62)		
Restenosis Rate In-Lesion Binary Restenosis	23.7% (14/59)	60.7% (34/56)	0.39 (0.24, 0.65)	-37.0 (-54.1, -19.9)
Mean Lumen Area at 6 month follow-up (IVUS)				
Means±SD (N)	7.04±2.38 (47)	4.85±2.88 (50)	N/A	(1.12, 3.26)
TLR-free at 6 months	84.6% (55/65)	36.9% (24/65)	2.29 (1.64, 3.20)	47.7 (32.8, 62.6)
TVR-free at 6 months	72.3% (47/65)	32.3% (21/65)	2.24 (1.53, 3.28)	40.0 (24.0, 56.0)
MACE-free at 6 months	70.8% (46/65)	32.3% (21/65)	2.19 (1.49, 3.22)	38.5 (22.3, 54.6)
Safety Measures				
In-Hospital MACE	1.5% (1/65)	0.0% (0/65)	3.00 (0.12, 72.31)	1.5 (-1.5, 4.6)
Out-of-Hospital MACE to 6 months	29.2% (19/65)	67.7% (44/65)	0.43 (0.29, 0.65)	-38.5 (-54.6, -22.3)
MACE to 30 days (cumulative)	3.1% (2/65)	1.5% (1/65)	2.00 (0.19, 21.52)	1.5 (-3.7, 6.8)
MACE to 6 months (cumulative)	29.2% (19/65)	67.7% (44/65)	0.43 (0.29, 0.65)	-38.5 (-54.6, -22.3)
Abrupt Closure to 30 days	0.0% (0/65)	0.0% (0/65)		
Subacute Closure to 30 days	0.0% (0/65)	0.0% (0/65)		
Stent Thrombosis to 30 days	0.0% (0/65)	0.0% (0/65)		
CVA to 30 days	0.0% (0/65)	0.0% (0/65)		
In-hospital Vascular Complications	10.8% (7/65)	10.8% (7/65)	1.00 (0.37, 2.69)	0.0 (-10.8, 10.8)
Vascular Complications to 6 months (cumulative)	12.3% (8/65)	12.3% (8/65)	(0.40, 2.50)	0.0 (-11.5, 11.5)
Late Thrombosis	3.1% (2/65)	0.0% (0/65)		3.1 (-1.1, 7.3)
Late Total Occlusion	13.8% (9/59)	1.5% (1/56)*	9.00 (1.17, 69.02)	12.3 (3.4, 21.2)

Numbers are % (counts/sample size) or Mean ± SD — CI = Confidence Interval

Relative Risk = p_1/p_2, $p_i = n_{i1}/n_i$ — SE = sqrt $\{(1-p_1/n_{11}+(1-p_2)/n_{21})\}$ — CI = RR*exp (± 1.96* SE)

Difference = p_1-p_2 — SE = sqrt $\{(p_1*q_1/n_1+p_2*q_2/n_2)\}$ — CI = Diff ± 1.96* SE

N/A = Not applicable

Lesion success = Lesion success was defined as the attainment of <50% residual stenosis (by QCA) using percutaneous method.

Device Success = Device success was defined as the attainment of a <50% residual stenosis using assigned treatment and delivery of the ribbon for the desired dwell time.

Procedure Success = Procedure success was defined as the attainment of a <50% residual stenosis by QCA and freedom from death, Q wave MI or emergent CABG.

Post-Procedure In-Lesion Percent Diameter Stenosis (% DS) = The % diameter stenosis post procedure was defined as (1-MLD/RVD) *100 as is identified within the stenotic segment ("in lesion"). Whenever possible, normal and minimal lesion diameters are calculated from two "orthogonal" projections. Range (min, max) measurement of smallest stenosis and largest stenosis, respectively.

Post Procedure In-Stent Percent Diameter Stenosis (% DS) = The stent % diameter stenosis post procedure was defined as (1-MLD-RVD) * 100 as is identified within the stent ("in stent"). Whenever possible, normal and minimal lesion diameters are calculated from two "orthogonal" projections. Range (min, max) measurement of smallest stenosis and largest stenosis, respectively.

Late Loss = Late loss is defined as the late change in dimensional minimal lumen diameter that occurred during the follow-up period measured by quantitative coronary angiography based on the average from two orthogonal views after the final post-dilatation to follow-up. Final MLD – FU MLD. Reported for in-stent.

Binary Restenosis = Angiographic restenosis ≥ 50% minimum lumen diameter stenosis at the follow-up angiogram. Restenosis is recorded for in lesion.

Mean Lumen Area = Average lumen area over the length of treated segment as measured by intravascular ultrasound at 6 months follow-up in mm^2.

TLR-free at 6 months = Target lesion revascularization was defined as a clinically driven repeat revascularization of a target lesion that was angiographically narrowed. The definition of "clinically driven" included a positive functional ischemia study, resting ischemic ECG changes in a distribution consistent with the target vessel, ischemic symptoms, and angiographic minimal lumen diameter stenosis ≥ 50% by QCA; revascularization of a target lesion with diameter stenosis ≥ 70% by QCA without either angina or a positive functional study was also considered clinically driven.

Table 8.3 Continued

TVR-free at 6 months = Target vessel revascularization was defined as a target lesion revascularization (defined above) or revascularization due to narrowing of any segment of the target vessel proximal or distal to the target lesion. This definition assumed that the entire vessel was vulnerable to late failure because of guide catheter or guidewire trauma or progression of disease remote from the treatment site. The target vessel revascularization definition required that: target vessel revascularization was clinically driven (as defined for the target lesion revascularization, see above). The angiographic core laboratory determined that the target lesion had a diameter stenosis of $\geq$ 50% by QCA or the clinical site reported a narrowing of another site in the target vessel with diameter stenosis $\geq$ 50%.

MACE-free at 6 months = MACE was defined as target vessel revascularization, Q wave myocardial infarction or cardiac death that could not be clearly attributed to a non-target vessel. Therefore, target vessel failure included any revascularization or adverse endpoints due to renarrowing of any segment of the target vessel. Target vessel failure was reported when: target vessel revascularization occurred (defined below); myocardial infarction occurred and the territory was not clearly other than that of the target vessel; or cardiac death occurred and could not be clearly attributed to a non-target vessel.

In-Hospital MACE = In-hospital MACE (Major Adverse Cardiac Events) were defined as cardiac death, target Q wave MI, and target *vessel* revascularization (CABG or PTCA of the target vessel) as determined by the independent Clinical Events Committee from index procedure through the hospital discharge.

Out-of-Hospital MACE = Out-of-hospital MACE (Major Adverse Cardiac Events) were defined as death, Q wave MI, and target vessel revascularization (CABG or PTCA of the target vessel) as determined by the independent Clinical Events Committee from discharge through the 6 month contact.

MACE to 30 days (cumulative) = The occurrence of any major adverse cardiac event including cardiac death, QWMI, CABG, or repeat PTCA within 30 days of the index procedure. One event should be reported per patient.

MACE to 6 months (cumulative) = The occurrence of any major adverse cardiac event including cardiac death, QWMI and target vessel revascularization that occurred from the index procedure to the 6 month follow-up. One event should be reported per patient.

Abrupt Closure = Abrupt closure is defined as the occurrence of new reduced flow (TIMI 0 or 1) of the target vessel and required rescue by another device or emergency surgery or resulted in myocardial infarction or death. Abrupt closure is related to the mechanical dissection (of the treatment site or other instrumental site), coronary thrombus, or severe spasm. Abrupt closure does not connote no re-flow in which the artery was patent but reduced flow persisted. Abrupt closure also does not connote transient closure unless a Class 2 or 3 MI or death occurred. Threatened abrupt closure was defined as a NHLBI dissection Grade B with a 50% diameter stenosis or any Grade C dissection or higher. Threatened closure was not used as a primary endpoint but was used to adjudicate the use of other devices.

Subacute Closure to 30 days = Subacute closure was defined as abrupt closure that had occurred after the index procedure was completed and the patient had left the catherization laboratory and was within 30 days of the index procedure.

Stent Thrombosis = Cardiac death, Q wave MI, angiographic total occlusion at follow-up or evidence of angiographic thrombus (core laboratory and investigator), reported at 30 days. In the absence of the QCA, total occlusion was adjudicated by the Clinical Events Committee.

CVA to 30 days = The occurrence of a new permanent stroke following the procedure within 30 days of the index procedure.

In-Hospital Vascular Complications = In-hospital vascular complications were defined as the occurrence of any of the following: hematoma at the access site of > 4 cm in maximum diameter, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, procedure-related blood transfusion, or vascular surgical repair between index procedure to discharge date of hospital stay.

Vascular Complications to 6 months (cumulative) = Vascular complications were defined as the occurrence of any of the following: hematoma at the access site of > 4 cm in maximum diameter, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, procedure related blood transfusion, or vascular surgical repair both in hospital from index procedure to discharge and out of hospital.

Late Thrombosis = Myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and in a newly implanted bypass graft at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.

Late Total Occlusion = Consists of Late Thrombosis and Total Occlusion.

* Additionally, the rates of late thrombosis and late total occlusion for the crossover group are 5.1% (2/39) and 12.8 (5/39), respectively.

Table 8.4: Major Adverse Cardiac Events – In-Hospital vs. Out-of-Hospital
All Patients Treated

	GAMMA-I			SCRIPPS-I			WRIST		
	Radiation (N=131)	Placebo (N=121)	All (N=252)	Radiation (N=29)	Placebo (N=31)	All (N=60)	Radiation (N=65)	Placebo (N=65)	All (N=130)
In-Hospital Complications									
MACE (Death, MI, Emergent CABG, TLR)*	2.3% (3)	3.3% (4)	2.8% (7)	0.0% (0)	0.0% (0)	0.0% (0)	1.5% (1)	0.0% (0)	0.8% (1)
Death (for WRIST: non-cardiac death only)	0.8% (1)	0.0% (0)	0.4% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Myocardial Infarction (Q or Non-Q)	2.3% (3)	2.5% (3)	2.4% (6)	0.0% (0)	0.0% (0)	0.0% (0)	10.8% (7)	7.7% (5)	9.2% (12)
Q Wave MI	0.8% (1)	0.8% (1)	0.8% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Non-Q Wave MI	1.5% (2)	1.7% (2)	1.6% (4)	0.0% (0)	0.0% (0)	0.0% (0)	10.8% (7)	7.7% (5)	9.2% (12)
Emergent CABG	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Target Lesion Revascularization	0.0% (0)	1.7% (2)	0.8% (2)	0.0% (0)	0.0% (0)	0.0% (0)	1.5% (1)	0.0% (0)	0.8% (1)
TL-CABG	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
TL-PTCA	0.0% (0)	1.7% (2)	0.8% (2)	0.0% (0)	0.0% (0)	0.0% (0)	1.5% (1)	0.0% (0)	0.8% (1)
Perforation	0.8% (1)	0.0% (0)	0.4% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Bleeding Complications	0.8% (1)	0.0% (0)	0.4% (1)	0.0% (0)	6.5% (2)	3.3% (2)	6.2% (4)	1.5% (1)	3.8% (5)
Vascular Complications	2.3% (3)	0.8% (1)	1.6% (4)	0.0% (0)	0.0% (0)	0.0% (0)	10.8% (7)	10.8% (7)	10.8% (14)
Hematologic Dyscrasia	0.0% (0)	0.0% (0)	0.0% (0)	N/A	N/A	N/A	N/A	N/A	N/A
CVA	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Acute Stent Thrombosis (to 30 days)	0.0% (0)	0.8% (1)	0.4% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Late Thrombosis	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	N/A	N/A	N/A
Late Total Occlusion	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	N/A	N/A	N/A
Out-of-Hospital Complications**									
MACE (Death, MI, Emergent CABG, TLR)	26.7% (35)	42.1% (51)	34.1% (86)	20.7% (6)	22.6% (7)	21.7% (13)	29.2% (19)	67.7% (44)	48.5% (63)
Death	2.3% (3)	0.8% (1)	1.6% (4)	0.0% (0)	0.0% (0)	0.0% (0)	4.6% (3)	6.2% (4)	5.4% (7)
Myocardial Infarction (Q or Non-Q)	9.9% (13)	4.1% (5)	7.1% (18)	6.9% (2)	3.2% (1)	5.0% (3)	9.2% (6)	7.7% (5)	8.5% (11)
Q Wave MI	4.6% (6)	2.5% (3)	3.6% (9)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Non-Q Wave MI	5.3% (7)	1.7% (2)	3.6% (9)	6.9% (2)	3.2% (1)	5.0% (3)	9.2% (6)	7.7% (5)	8.5% (11)
Emergent CABG	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	N/A	N/A	N/A
Target Lesion Revascularization	24.4% (32)	40.5% (49)	32.1% (81)	17.2% (5)	22.6% (7)	20.0% (12)	15.4% (10)	63.1% (41)	39.2% (51)
TL-CABG	9.9% (13)	20.7% (25)	15.1% (38)	3.4% (1)	3.2% (1)	3.3% (2)	7.7% (5)	6.2% (4)	6.9% (9)
TL-PTCA	19.8% (26)	25.6% (31)	22.6% (57)	13.8% (4)	19.4% (6)	16.7% (10)	9.2% (6)	61.5% (40)	35.4% (46)
Perforation	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Bleeding Complications	1.5% (2)	0.8% (1)	1.2% (3)	0.0% (0)	0.0% (0)	0.0% (0)	N/A	N/A	N/A
Vascular Complications	0.8% (1)	0.8% (1)	0.8% (2)	0.0% (0)	0.0% (0)	0.0% (0)	3.1% (2)	3.1% (2)	3.1% (4)
Hematologic Dyscrasia	0.8% (1)	1.7% (2)	1.2% (3)	NA	NA	NA	N/A	N/A	N/A
CVA	0.8% (1)	2.5% (3)	1.6% (4)	0.0% (0)	3.2% (1)	1.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Acute Stent Thrombosis (to 30 days)	0.8% (1)	0.8% (1)	0.8% (2)	3.4% (1)	0.0% (0)	1.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Late Thrombosis	5.3% (7)	0.8% (1)	3.2% (8)	0.0% (0)	0.0% (0)	0.0% (0)	3.1% (2)	0.0% (0)	1.5% (2)
Late Total Occlusion***	12.6% (14)	5.8% (6)	9.3% (20)	3.6% (1)	0.0% (0)	1.7% (1)	13.8% (9)	1.5% (1)	7.7% (10)

* MACE for GAMMA-I and SCRIPPS-I = Death, MI (Q Wave and non-Q Wave), Emergency CABG and TLR)
MACE for WRIST = Cardiac death, Q Wave MI, Emergency CABG and TVR.
** Out of Hospital Complications: GAMMA-I: to 270 days
SCRIPPS-I: to 180 days
WRIST: 180 days +/- 30 days
***Based on follow-up angiogram.

8.1 Additional Late Thrombosis Information

Summarized in Table 8.5 is the late thrombosis information based on data collected from the GAMMA-I, SCRIPPS-I and WRIST trials up to June 2000, which is beyond the primary study endpoints (See Table 8.5 for further details).

Table 8.5: Late Thrombosis GAMMA-I, SCRIPPS-I, WRIST*

	Radiation	Placebo
GAMMA-I	5.3% (7/131)	0.8% (1/121)
SCRIPPS-I	0.0% (0/29)	0.0% (0/31)
WRIST	6.2% (4/65)	1.5% (1/65)
WRIST (Crossover)	5.1% (2/39)	–
TOTAL	**4.9% (13/264)**	**0.9% (2/217)**

GAMMA-I: Results in this table represent data at 1.5 years. Patients with new stents received 8 weeks of antiplatelet therapy.
SCRIPPS-I: Results in this table represent data at 3 years. Patients with new stent received 2 weeks of antiplatelet therapy.
WRIST: Results in this table represent data at 2 years. All patients received 4 weeks of antiplatelet therapy.
Late Thrombosis = Myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and in a newly implanted bypass graft at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.

Additionally, the use of prolonged antiplatelet therapy was evaluated during the SCRIPPS-III and WRIST Plus registry trials. During the SCRIPPS-III trial, patients who received a new stent are placed on 12 months of antiplatelet medication and 6 months if no new stent is placed. During the WRIST Plus trial all patients received 6 months of antiplatelet medication. A summary of late thrombosis events up to August 18, 2000 can be found in Table 8.6. Note: The follow-up in these two trials is not yet complete, since the studies are still on-going.

Table 8.6
Survival Free From Late Thrombosis: SCRIPPS-III, WRIST Plus trials
Event-Free Survival; All Patients Treated (n=534)

Time After Initial Procedure (days)	0	30	60	90	120	150	180	210
Effective Sample Size	508.5	481.5	447.5	413.5	379.0	333.5	269.5	206.0
Number Censored	19	35	31	35	34	57	71	54
Number of Events	0	1	1	0	0	0	1	0
% Survival	100%	100%	99.79%	99.56%	99.56%	99.56%	99.56%	99.17%
% Failure	0.00%	0.00%	0.21%	0.44%	0.44%	0.44%	0.44%	0.83%
% Peto Survival SE	0.00%	0.00%	0.21%	0.32%	0.33%	0.35%	0.38%	0.57%
% Failure 95% Lower Conf. Limit	0.00%	0.00%	0.03%	0.10%	0.10%	0.09%	0.08%	0.22%
% Failure 95% Upper Conf. Limit	0.00%	0.00%	1.53%	1.81%	1.92%	2.05%	2.36%	3.18%

9. Patient Selection and Treatment

9.1 Individualization of Treatment

The risks and benefits described above should be carefully considered for each patient before use of intravascular brachytherapy. Patient selection factors to be assessed should include a judgement regarding risk of prolonged anticoagulation. Intravascular brachytherapy with stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease, see CONTRAINDICATIONS).

Premorbid conditions that increase the risk of a poor initial result and the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed. The relation of baseline and procedural variables to Major Adverse Cardiac Events (MACE) was examined. The only significant univariate predictors of MACE in the GAMMA-I trial were lesion length and post-procedural mean in-stent minimum lumen diameter (MLD). MACE was more likely with longer lesions and smaller MLD.

9.2 Use in Special Populations

The safety and effectiveness of the Cordis Checkmate System has not been established because it has not been adequately studied in:

- Patients with coronary artery **reference vessel diameter < 2.75 mm and > 4.0 mm.**
- Patients with target **lesions longer than 45 mm.**
- Patients with **vascular disease other than in-stent** coronary artery stenosis.
- Patients with recent **acute myocardial infarction** and there is evidence of thrombus.
- Patients with **lesions located** in the left main coronary artery, saphenous vein grafts or internal mammary arteries.

10. Patient Counseling Information

Physicians should consider the following in counseling the patient about this device:

- Discuss the risks associated with exposure to radiation.
- Discuss the risk/benefit issues for this particular patient.
- Discuss alterations to current lifestyle immediately following the procedure and over the long term.

11. How Supplied

STERILE. The Checkmate Catheter, dummy ribbon and source lumen plug are sterile; these devices are sterilized with Ethylene Oxide (EtO). The Checkmate Catheter is non-pyrogenic. Do not use if the package is opened or damaged.

CONTENTS. One (1) Checkmate Catheter, one (1) dummy ribbon and one (1) source lumen plug.

STORAGE. Store in a cool, dry, dark place.

Table 11.1
Device Specification

	Checkmate Catheter	Dummy Ribbon
Device Specifications	Overall Length: 230 cm Usable Length: 145 cm Prox. Shaft O.D.: 0.068" (5.1F) Dist. Shaft O.D. : 0.049" (3.7F)	Overall Length: 238.6 cm Ribbon O.D.: 0.030" Simulated Source Length: 6-seed: 23 mm 10-seed: 39 mm 14-seed: 55 mm 18-seed: 71 mm 22-seed: 87 mm Ribbon Color: Yellow
Compatible With	≥ 7F Guiding Catheter 0.014" Guidewire Cordis Checkmate Delivery System	Cordis Checkmate Delivery System

12. Operator Manual

12.1 Materials Required

The following materials are required to perform a Checkmate intravascular brachytherapy procedure after a successful revascularization procedure has been performed:

Quantity	Material
	Appropriate guiding catheter(s) (See Table 11.1, Device Specification)
1	Guidewire (See Table 11.1, Device Specification)
1	Cordis Checkmate Delivery System (with Ir-192 source ribbon)
1	Rotating luer connector
As required	Portable lead shield(s)
As required	Radiation detection equipment

12.2 Preparation and Inspection

Warnings

- Avoid performing the intervention and/or injuring a vessel segment outside of the radiation treatment area.

Precautions

- **For single use only.** Do not resterilize or reuse.
- The hub of the Checkmate Catheter is no longer sterile after connection to non-sterile devices. Following contact with a non-sterile source ribbon, the source lumen is no longer sterile.
- Do NOT use after the "Use By" date as sterility and/or function may be compromised.
- Carefully inspect the sterile package before opening. If the package is damaged, the contents may not be sterile and may cause infection.
- The Checkmate Catheter contains a closed ended source lumen.. DO NOT infuse any liquids through the source lumen. Maintain dry conditions.

12.2.1 Checkmate Delivery Device

Step	Action
1	Follow the instructions provided with the Cordis Checkmate Delivery System for procedures associated with preparing the Ir-192 source ribbon and the delivery device.

12.2.2 Checkmate Catheter

Step	Action
1	Carefully remove the Checkmate Catheter and dummy ribbon assembly from its protective coil packaging.
2	Inspect the catheter/dummy ribbon assembly to ensure it is not damaged. If the catheter or dummy ribbon are damaged, discard and replace the catheter and dummy ribbon.
3	Visually inspect the distal end of the Checkmate Catheter to verify that the dummy ribbon is loaded and fully inserted into the end of the catheter source lumen. Insert the source lumen plug packaged with the Checkmate Catheter into the catheter hub to secure the dummy ribbon in place.

12.3 Recommended Procedure (See also the Instructions for Use of the Checkmate Delivery System)

12.3.1 Treatment Prerequisite

Step	Action
1	Perform revascularization of the previously stented target lesion using current interventional techniques. NOTE: Refer to "System Compatibility" section for catheter size and compatibility information.
2	Verify satisfactory result with angiography and/or IVUS. NOTE: It is important that an optimal redilatation of the restenotic lesion is achieved prior to intravascular brachytherapy.
3	Maintain the position of the procedure guidewire across the target lesion.

12.3.2 Dosimetry (Also refer to the Instructions for Use of the Cordis Checkmate Delivery System.)

Warnings:

- The biological risks of doses above 3000 cGy to the near wall have not been established.

Step	Action
1	Using intravascular ultrasound (IVUS), measure the distance from the center of the IVUS catheter to the leading edge of the tunica media. Measure a minimum of three (3) sites along the stent vessel segment.
2	Determine the maximum and minimum source to target distances along the stented vessel.
3	Calculate the dwell time to deliver the desired dose by using the maximum and minimum source to target distances and the specific activity level of the Ir-192 source from the Certificate of Activity (Bill of Lading) supplied with the Checkmate Delivery System. • The dwell time should be calculated such that a dose of 800 cGy is delivered to the target farthest from the radiation source provided that no more than 3000 cGy is delivered to the target closest to the radiation source. • If the dose to the near wall is calculated to be more than 3000 cGy, the dwell time should be based on delivering 3000 cGy to the near wall. In this case, calculate and use the dose to be delivered to the far wall.
4	Document the dose calculations.

12.3.3 Checkmate Catheter Introduction and Positioning

Precautions:

- Care should be taken when inserting the Checkmate Catheter into the hemostasis valve and during tightening of the hemostasis valve in order to avoid crimping or kinking of the catheter.

- DO NOT advance the Checkmate Catheter within the vasculature unless it is preceded by a guidewire. The catheter can disengage from the guidewire if it is pushed past the guidewire tip. If this occurs, remove the catheter while leaving the guidewire in place and repeat steps 2-4 for catheter introduction.

- DO NOT advance the catheter over the floppy portion of the guidewire as the guidewire may prolapse when the catheter is withdrawn. If this occurs, attempt to resolve the prolapse by gently pulling back on the guidewire while simultaneously advancing the catheter. If the prolapse persists, disengage the catheter from the guidewire by continuing to advance the catheter while gently pulling back on the guidewire. Remove the catheter (or remove the guidewire and catheter as a unit).

- DO NOT flush the source lumen with saline or other liquids. If the source lumen gets wet, remove the Checkmate Catheter and discard.

Step	Action
1	Attach a hemostasis valve to the luer port of the guiding catheter positioned in the vasculature.
2	Under fluoroscopy, verify that the procedure guidewire is correctly positioned across the target lesion.
3	Protect the proximal end of the Checkmate Catheter from blood or fluid contact.
4	Insert the proximal end of the indwelling guidewire into the distal end of the Checkmate Catheter. The guidewire will exit through the port on the catheter tip. NOTE: Before inserting the Checkmate Catheter, wipe the proximal end of the guidewire with a saline soaked gauze to remove any excess contrast medium.
5	Under fluoroscopy, advance the Checkmate Catheter over the guidewire. Position the catheter across the target lesion using the radiopaque markers on the catheter and dummy ribbon to define the target lesion. NOTE: It is recommended that the treatment zone includes a margin of approximately 3-5 mm (1-1.33 seeds) on either side of the target lesion (see illustration). NOTE: Care should be taken to avoid rotating the Checkmate Catheter as it is advanced over the guidewire. Such action may cause the guidewire to wrap around the catheter making further advancement difficult.
6	Make any adjustments to the catheter position when the dummy ribbon is in place. When satisfied that the catheter is correctly positioned across the intended treatment site, tighten the hemostasis valve to maintain the catheter position.
7	Remove the source lumen plug. Withdraw the dummy ribbon proximal to the hemostasis valve and re-insert to verify the ability to access the treatment site.
8	Remove the dummy ribbon from the Checkmate Catheter and discard .
9	Visually check that there are no kinks in the proximal section of the Checkmate Catheter.
10	Ensure that an ACT taken just prior to the radiation dwell time is greater than 300 sec. (> 350 sec. if a Hematec analyzer is used).

Illustration

12.3.4 Intravascular Radiation Therapy Procedure

Warnings:

- Do not completely withdraw the source ribbon from the shielded delivery device. If this occurs, reinsert the source ribbon into the delivery device. Notify the institutional radiation safety officer immediately and follow the established radiation safety protocol.

Precautions

- The Checkmate Delivery System and the transport cart are **NON-STERILE** and should remain outside of the sterile field.
- It is recommended that survey meter readings are recorded several times during the procedure to ensure that the radioactivity remains within an acceptable level.
- Maintain visual and audio contact with the patient during the intravascular brachytherapy procedure.
- Maintain hemodynamic monitoring of the patient during the intravascular brachytherapy procedure.
- If excessive resistance is encountered during the insertion, retract the source ribbon back into the Checkmate Delivery Device. Do not re-advance the radioactive source ribbon until the cause of resistance has been remedied, or a new Checkmate Catheter has been introduced.
- If significant symptoms of ischemia occur, the treatment may be fractionated. Rapidly retract the source ribbon into the Checkmate Delivery Device. Record the exposure time. Resolve the ischemic symptoms before re-introducing the source ribbon for the remaining treatment time. Fractionation of treatment time increases the radiation exposure to the radiation oncologist and to the patient. Use fractionation only if significant ischemia occurs.
- The proximal end and the source lumen of the catheter are no longer sterile after connection to the Checkmate Delivery Device. Handle per site procedures.

Step	Action
1	Transport the Checkmate Delivery System to a location within range of the patient but outside of the sterile field.
2	Connect the catheter hub to the rotating luer connector of the delivery device. NOTE: DO NOT rotate the catheter.
3	Transport the portable lead shield(s) to the side(s) of the patient to minimize radiation exposure to attending personnel. Position the shields as defined by institutional radiation safety procedures.
4	When ready to initiate the intravascular brachytherapy procedure, all personnel should be positioned behind appropriate shielding as defined by institutional radiation safety procedures.
5	Deploy the source ribbon per the Instructions for Use of the Checkmate Delivery System. Verify the position of the source ribbon with the fluoroscope, utilizing the radiopaque markers and contrast injection. Secure the source ribbon in place.
6	Begin timing of the dwell time as soon as the radioactive source ribbon is positioned.
7	Monitor the patient closely during the treatment time with the Ir-192 source ribbon.
8	At the conclusion of the dwell time, withdraw the source ribbon per the Instructions for Use of the Checkmate Delivery System. Use a survey meter to verify that the source ribbon is properly contained within the Checkmate Delivery Device. Record the measurements.
9	Personnel may move from behind the radiation shielding. NOTE: Standard shielding practices for fluoroscopy must still be followed.
10	Disconnect the catheter from the Checkmate Delivery Device. NOTE: Placement of a new stent during the radiation procedure has been associated with a higher rate of late thrombosis in comparison to the placebo arm. Every attempt should be made to avoid new stent placement in the irradiated area. However, if placement of a new stent was necessary, it is recommended that the patient be placed on antiplatelet therapy.
11	Transport the Checkmate Delivery Device to a secure, restricted access area that has been designated for and meets the requirements for radioactive storage.

12.4 Withdrawal Procedure

Precautions

- DO NOT advance the catheter over the floppy portion of the guidewire as the guidewire may prolapse on withdrawal of the catheter. If this occurs, attempt to resolve the prolapse by gently pulling back on the guidewire while simultaneously advancing the catheter. If the prolapse persists, disengage the catheter from the guidewire by continuing to advance the catheter while gently pulling back on the guidewire. Remove the catheter (or remove the guidewire and catheter as a unit).

- If the radioactivity readings register above the acceptable limits, notify the institutional safety officer immediately and follow the established institutional radiation safety protocol.

Step	Action
1	Remove and discard the Checkmate Catheter.
2	Use a survey meter to survey the patient and the catheter for any radiation. Record the measurements.
3	Perform a post procedure angiogram if required.
4	Remove the guidewire, guiding catheter and the sheath introducer from the vasculature per standard techniques.
5	Close the arterial opening per desired technique.

12.5 Return Procedure of Checkmate Delivery Device and Ir-192 Source Ribbon

Step	Action
1	Refer to the return shipping guidelines supplied with the Checkmate Delivery System.

13 References

P. Teirstein, V. Massullo, S. Jani, et al., "Catheter-Based Radiation Therapy to Inhibit Restenosis after Coronary Stenting", NEJM, v. 336, n. 24, pp. 1697-1703.

Date of Labeling Modification: November, 2000

14 Disclaimer

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15 Revision History

Date	Rev	
June 1999	1	First revision of final draft labeling.
May 2000	2	Change name from IRT to Checkmate Update clinical results
June 2000	3	Change Table 7.1 to Peto Results Update Indications for Use, Contraindications & Warnings per recommendation of the FDA Panel.
July 2000	4	Update per meeting with FDA
October 2000	5	Updated in response to deficiency questions
November 2000	6	Update per FDA request

Cordis Checkmate™ Delivery System

Instructions for Use

Caution: Federal Law restricts this device to sale by or on the order of a physician.

Table of Contents

1. Device Description

The Cordis Checkmate Delivery System is a component of the Cordis Checkmate System; the other component of the Cordis Checkmate System is the Cordis Checkmate Catheter (see also Section 12.1). The Cordis Checkmate Delivery System (this package) includes:

1. Iridium 192 (Ir-192) Source Ribbon
   - This ribbon contains a strand of radioactive seeds (6, 10 or 14) with a proximal and distal radiopaque marker.

2. Delivery Device
   - Provides the lead shielded housing of the Ir-192 source ribbon during shipment, storage and transportation to and from cath lab. The radioactive section of the source ribbon is completely encased in the shielded delivery device.
   - The proximal end of the source ribbon protrudes from the body of the delivery device and is coiled and held next to the delivery device when not in use.
   - Both ends of the delivery device are protected by latched end caps.
   - A fitting located on the proximal end of the delivery device secures the ribbon in place when not in use.
   - A threaded cap is located on the distal end of the delivery device when not in use. When in use, the threaded cap is replaced with a luer connector.
   - The source ribbon is fed by hand from the proximal end of the delivery device into the Checkmate Catheter, which is attached to the luer connector.
   - Each delivery device is supplied with a Certificate of Activity (Bill of Lading) detailing the radioactive levels and decay profile for the isotope contained within and the "Use By" date of the radioactive source ribbon.

2. Indications

The Cordis Checkmate Delivery System is intended for the delivery of therapeutic doses of gamma radiation for the purpose of reducing in-stent restenosis. The system is for use in the treatment of native coronary arteries with in-stent restenosis following percutaneous revascularization using current interventional techniques.

- This system is for use in vessels 2.75 – 4.0 mm in diameter and for lesions up to and including 45 mm in length.

3. Contra-indications

Intracoronary radiation therapy is generally contraindicated in the following patient types:

- Patients in whom antiplatelet and/or anticoagulant therapy is contraindicated.

4. Warnings

Avoid placement of a new stent during the radiation procedure as it has been associated with a higher rate of late thrombosis in comparison to the placebo arm. Every attempt should be made to avoid new stent placement in the irradiated area. However, if placement of a new stent was necessary, it is recommended that the patient be placed on antiplatelet therapy for 12 months. If no new stent was placed it is recommended to prescribe antiplatelet therapy for 6 months (see also Sections 8.0 and 8.1).

- This product contains a gamma radiation emitting source and should be handled only by authorized personnel.
- The Cordis Checkmate System should not be used for indexing procedures as it may result in overexposure of overlapping treatment areas.
- Verify the source location if the deliver device, cart, or catheter are moved or if the patient shifts position during the treatment time to ensure that proper source placement is maintained.

5. Precautions See also Section 12, "Operator Manual"

5. 1 Precautions General

- The Cordis Checkmate Delivery System should only be used in combination with the Cordis Checkmate Catheter.
- Only physicians who have received adequate training should perform intravascular brachytherapy.
- Intravascular brachytherapy should only be performed at hospitals with the appropriate licensing from the governing nuclear regulatory agency for use of radiation for intravascular therapeutic purposes.
- Intravascular brachytherapy should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Do not expose the source ribbon to solvents (e.g. alcohol, hydrogen peroxide).
- If required, the outside of the delivery device may be wiped with a cloth and alcohol solution. Do not pour liquids directly on the device.
- The Checkmate Delivery Device weighs approx. 45 lbs. Use caution when removing the delivery device from the transport container, lifting it or positioning it, to prevent injury. (Two person lift.)
- The delivery device should only be placed on tables or carts (with locking wheels) capable of supporting the device's weight. If accidentally dropped from the table or cart, survey the delivery device to ensure the source is still in the correct position.

5.2 Radiation Precautions

- Follow the As Low As Reasonably Achievable (ALARA) policy guidelines.
- Follow the site specific radiation safety procedures.
- When not in use, the Ir-192 source ribbon and delivery device should be stored in a secure, locked area with restricted access separate from other medical devices. Radiation safety regulations for storage of radioactive material should be strictly adhered to.
- Use radiation detection instruments (Geiger counter or appropriate survey meter) while inspecting, unpacking and using Ir-192 source ribbons.
- Use appropriate radiation detection methods (e.g. film badges, ring dosimeters) when handling radioactive source ribbons per the institutional radiation safety protocol and as defined by the governing nuclear regulatory agency.
- Keep the Ir-192 source ribbon in the delivery device at all times except during use.
- Avoid contact with the seeds in the radioactive source ribbon or any unnecessary radiation exposure. Always use long forceps or tongs when handling Ir-192 source ribbons.
- If a seed is cut accidentally during an emergency procedure, be careful in disposing of the damaged seed (use an appropriately shielded container). Check the tools and area for possible contamination and survey the area thoroughly. Do not use tools again until they are completely clean (free of contamination).
- Use appropriate lead shielding when handling Ir-192 source ribbons.
- Survey the area where the Ir-192 source ribbons are used thoroughly after each use and make sure that no seeds or ribbons are lost. Each Ir-192 seed is a radioactive source and, as such, should be accounted for.
- In case of loss of seed(s) or an accident involving the seed(s), it should be reported immediately to the proper Nuclear Regulatory Agency.
- For safe handling of radioactive sources, three factors (time, distance and shielding) should be observed:

  Time: Less time, less radioactive exposure.
  Distance: More distance from the radioactive source, less radiation exposure.
  Shielding: Better shielding (thicker lead or lead glass shielding), less radiation exposure.

6. Special Considerations

Safety and effectiveness has not been demonstrated in the following populations:

- Patient with previous intravascular brachytherapy of the same vessel segment or previous radiation treatment in the immediate vicinity.
- Patients who are pregnant.
- Patients with known genetic radiation sensitivity disorders (e.g. ataxia-leangiectasia, etc.)
- Patients with saphenous vein graft disease.

7 Adverse Events

7.1 Observed Adverse Events

A total of 252 patients were enrolled in a single multi-center randomized clinical trial (GAMMA-I trial) to evaluate the use of the Cordis Checkmate System for treatment of in-stent restenosis. These patients form the basis for the reported observed events (see Clinical Studies).

Additionally, data is provided on the SCRIPPS-I trial (single center, randomized trial, 60 patients) and the WRIST trial (single center, randomized trial, 130 patients). Both studies used the Ir-192 Source Ribbon for treatment of in-stent restenosis.

Table 7.1 Major Adverse Cardiac Events (to 270 days)
All patients in GAMMA-I Trial (N=252)

	Radiation (N=131)	Placebo (N=121)	Relative Risk [95% CI]	Difference [95% CI]
Any MACE (Death, MI, Em. CABG, TLR)	28.2% (37/131)	43.8% (53/121)	0.64 [0.46, 0.90]	-15.6% [-27.3%, -3.8%]
Death	3.1% (4/131)	0.8% (1/121)	3.69 [0.49, 28.03]	2.2% [-1.1%, 5.6%]
Myocardial Infarction (Q or Non-Q)	12.2% (16/131)	6.6% (8/121)	1.85 [0.83, 4.10]	5.6% [-1.5%, 12.7%]
Q Wave MI	5.3% (7/131)	3.3% (4/121)	1.62 [0.49, 5.33]	2.0% [-3.0%, 7.0%]
Non-Q Wave MI	6.9% (9/131)	3.3% (4/121)	2.08 [0.68, 6.40]	3.6% [-1.8%, 8.9%]
Emergent CABG	0.0% (0/131)	0.0% (0/121)	- [-,-]	0.0% [0.0%, 0.0%]
Target Lesion Revascularization	24.4% (32/131)	42.1% (51/121)	0.58 [0.41, 0.83]	-17.7% [-29.2%, -6.3%]
TL-CABG	9.9% (13/131)	20.7% (25/121)	0.48 [0.26, 0.88]	-10.7% [-19.6%, -1.9%]
TL-PTCA	19.8% (26/131)	27.3% (33/121)	0.73 [0.46, 1.14]	-7.4% [-17.9%, 3.0%]
Perforation	0.8% (1/131)	0.0% (0/121)	- [-,-]	0.8% [-0.7%, 2.3%]
Bleeding Complications	2.3% (3/131)	0.8% (1/121)	2.77 [0.32, 23.91]	1.5% [-1.6%, 4.5%]
Vascular Complications	3.1% (4/131)	1.7% (2/121)	1.85 [0.35, 9.66]	1.4% [-2.3%, 5.1%]
Hematological Dyscrasia	0.8% (1/131)	1.7% (2/121)	0.46 [0.04, 4.76]	-0.9% [-3.6%, 1.8%]
CVA	0.8% (1/131)	2.5% (3/121)	0.31 [0.04, 2.58]	-1.7% [-4.9%, 1.4%]
Acute Stent Thrombosis (to 30 days)	0.8% (1/131)	1.7% (2/121)	0.46 [0.04, 4.76]	-0.9% [-3.6%, 1.8%]
Late Thrombosis	5.3% (7/131)	0.8% (1/121)	6.47 [0.81, 51.79]	4.5% [0.3%, 8.7%]
Late Total Occlusion	12.6% (14/111)	5.8% (6/103)	2.17 [0.87, 5.42]	6.8% [-0.8%, 14.4%]

Numbers are % (counts/sample size) or Mean ± SD. CI = Confidence Interval
Relative Risk = Radiation/Placebo SE = sqrt $\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}$ CI = RR*exp(±1.96*SE)
Difference = Radiation – Placebo SE = sqrt $(p_1*q_1/n_1+p_2*q_2/n_2)$ CI = Diff±1.96*SE

As shown in Table 7.1, 5 patients died during the GAMMA-I trial. The 5 deaths occurred between 0 and 264 days post radiation and were due to: cardiac tamponade (n=1), hemorrhage following by-pass surgery (n=1), sudden cardiac death (n=2) and suicide (n=1). There were no device delivery failures and there were 11 cases of stent thrombosis, 3 acute stent thrombosis and 8 late thrombosis.

Table 7.2 Major Adverse Cardiac Events (to 180 days)
All patients in SCRIPPS-I Trial (N=60)

	Radiation (N=29)	Placebo (N=31)	Relative Risk [95% CI]	Difference [95% CI]
Any MACE (Death, MI, Em. CABG, TLR)	20.7% (6/29)	22.6% (7/31)	0.92 [0.35, 2.42]	-1.9% [-22.7%, 18.9%]
Death	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Myocardial Infarction (Q or Non-Q)	6.9% (2/29)	3.2% (1/31)	2.14 [0.21, 21.40]	3.7% [-7.5%, 14.8%]
Q Wave MI	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Non-Q Wave MI	6.9% (2/29)	3.2% (1/31)	2.14 [0.21, 21.40]	3.7% [-7.5%, 14.8%]
Emergent CABG	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Target Lesion Revascularization	17.2% (5/29)	22.6% (7/31)	0.76 [0.27, 2.14]	-5.3% [-25.5%, 14.8%]
TL-CABG	3.4% (1/29)	3.2% (1/31)	1.07 [0.07, 16.68]	0.2% [-8.9%, 9.3%]
TL-PTCA	13.8% (4/29)	19.4% (6/31)	0.71 [0.22, 2.27]	-5.6% [-24.3%, 13.2%]
Perforation	0.0% (0/29)	0.0% (0/31)	-[-, -]	0.0% [-,-]
Bleeding Complications	0.0% (0/29)	6.5% (2/31)	0.00 [-,-]	-6.5% [-15.1%, 2.2%]
Vascular Complications	0.0% (0/29)	0.0% (0/31)	- [-,-]	0.0% [-,-]
CVA	0.0% (0/29)	3.2% (1/31)	0.00 [-,-]	-3.2% [-9.4%, 3.0%]
Acute Stent Thrombosis (to 30 days)	3.4% (1/29)	0.0% (0/31)	- [-,-]	3.4% [-3.2%, 10.1%]
Late Thrombosis	0.0% (0/29)	0.0% (0/31)	-[-,-]	0.0% [-,-]
Late Total Occlusion	3.6% (1/28)	0.0% (0/28)	-[-,-]	3.6% [-3.3%, 10.5%]

Numbers are % (counts/sample size) or Mean ± SD. CI = Confidence Interval
Relative Risk = Radiation/Placebo SE = sqrt $\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}$ CI = RR*exp(±1.96*SE)
Difference = Radiation – Placebo SE = sqrt $(p_1*q_1/n_1+p_2*q_2/n_2)$ CI = Diff±1.96*SE
Late total occlusions were those occlusions in a patient who had angiographic documentation of 100% stenosis at the target site 31 days or more after the index procedure.

As shown in Table 7.2, there were no deaths in the SCRIPPS-I trial. There were no device delivery failures and there was 1 acute stent thrombosis.

Table 7.3 Major Adverse Cardiac Events (to 180 days +/- 30 days)
All patients in WRIST Trial (N=130)

	Radiation (N=65)	Placebo (N=65)	Relative Risk [95% CI]	Difference [95% CI]
Any MACE (Death, MI, Em. CABG, TLR)	29.2% (19/65)	67.7% (44/65)	0.43 [0.29, 0.65]	-38.5% [-54.6%, -22.3%]
Death	4.6% (3/65)	6.2% (4*/65)	0.75 [0.18, 3.22]	-1.5% [-9.4%, 6.4%]
Myocardial Infarction (Q or Non-Q)				
Q Wave MI	0.0% (0/65)	0.0% (0/65)	- [-,-]	0.0% [-,-]
Non-Q Wave MI	16.9% (11/65)	12.3% (8/65)	1.38 [0.59, 3.20]	4.6% [-7.7%, 16.9%]
Target Lesion Revascularization	15.4% (10/65)	63.1% (41/65)	0.24 [0.13, 0.44]	-47.7% [-62.6%, -132.8%]
CABG	7.7% (5/65)	6.2% (4/65)	1.25 [0.35, 4.45]	-1.5% [-7.3%, 10.4%]
PTCA	9.2% (6/65)	61.5% (40/65)	0.15 [0.07, 0.33]	-52.3% [-66.3%, -38.3%]
Vascular Complications	12.3% (8/65)	12.3% (8/65)	1.00 [0.40, 2.50]	0.0% [-11.5%, 11.5%]
TVR (not involving target lesion)	12.3% (8/65)	4.6% (3/65)	2.67 [0.74, 9.61]	7.7% [-1.9%, 17.3%]
CVA	0.0% (0/65)	0.0% (0/65)	- [-,-]	0.0% [-,-]
Subacute Closure (to 30 days)	0.0% (0/65)	0.0% (0/65)	- [-,-]	0.0% [-,-]
Late Thrombosis**	3.1% (2/65)	0.0% (0/65)	- [-,-]	3.1% [-1.1%, 7.3%]
Late Total Occlusion**	13.8% (9/65)	1.5% (1/65)	9.00 [1.17, 69.02]	12.3% [3.4%, 21.2%]

Numbers are % (counts/sample size) or Mean ± SD. CI = Confidence Interval
Relative Risk = Radiation/Placebo SE = sqrt $\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}$ CI = RR*exp(±1.96*SE)
Difference = Radiation – Placebo SE = sqrt $(p_1*q_1/n_1+p_2*q_2/n_2)$ CI = Diff±1.96*SE

* One patient died on day 212 and one on day 214.
** Additionally, the rates of late thrombosis and late total occlusion for the crossover group are 5.1% (2/39) and 12.8% (5/39), respectively.

As shown in Table 7.3, 7 patients died during the WRIST trial. The 7 deaths occurred between 0 and 214 days post radiation, all were cardiac deaths. There were no device delivery failures and there were 2 cases of late thrombosis.

7.2 Potential Adverse Events

Adverse events (in alphabetical order) which may be associated with intracoronary radiation treatment (including those listed in Table 7.1).

- Acute myocardial infarction
- Allergic reaction
- Aneurysm
- Arrhythmias, including VF and VT
- Death
- Dissection
- Drug reactions to antiplatelet agents/contrast medium
- Embolization
- Emergent Coronary Artery Bypass Surgery
- Hematological dyscrasia
- Hemorrhage, requiring transfusion
- Hypotension/Hypertension
- Infection and/or pain at the access site
- Ischemia, myocardial
- Malignant or pre-malignant transformation
- Perforation
- Pseudoaneurysm
- Restenosis of the radiated segment
- Spasm, coronary artery
- Stent embolization
- Stent thrombus/occlusion (acute, late)
- Stroke/cerebrovascular accident
- Total occlusion of coronary artery
- Vascular complications (e.g. fibrosis, necrosis, intimal proliferation)

For adverse events associated with antiplatelet and/or anticoagulant therapy, refer to the manufacturer's Instructions for Use.

56

8. Clinical Studies

GAMMA-I Trial (Pivotal Study)

This was a multi-center, prospective, randomized, double-blind trial designed to evaluate the safety and effectiveness of localized radiation therapy following percutaneous revascularization using current interventional techniques in patients with in-stent restenosis. A total of 252 patients were treated at 12 US investigational centers.

Primary Endpoint: The primary endpoint for the GAMMA-I trial was a composite of major adverse cardiac events including death, Q-wave and non-Q-wave myocardial infarction (MI), emergent CABG and target lesion revascularization (TLR) at 9 months post-procedure. **TLR was defined** as any clinically driven revascularization of the target lesion using either bypass surgery or percutaneous (i.e. angioplasty) techniques. An independent Clinical Events Committee, blinded to treatment assignment, adjudicated all major clinical endpoints for the GAMMA-I trial.

Patients Studied: Patients with in-stent restenosis of native coronary arteries, 2.75 – 4.0 mm in diameter and $\leq$ 45 mm in length, treated with current interventional techniques were admitted to the GAMMA-I trial.

Methods: Patients with in-stent restenosis underwent redilatation of the restenosis using current interventional techniques including high pressure (> 12 atmospheres) balloon inflation with a balloon-to-artery ratio of 1-1.2:1. If by angiography or ultrasound, a <30% residual stenosis was not obtained after this vigorous dilatation, or if a significant dissection was created inside the stent or the stent border, or if the restenotic lesion was at the stent border, another one or two approved non-coil stents were implanted as needed within and/or overlapping the original stent to cover the restenotic segments. New stents were optimally dilated using routine techniques.

Immediately after successful coronary intervention, the Cordis Checkmate Catheter and dummy ribbon were introduced over the indwelling guidewire, using the catheter's rapid exchange tip. After the Checkmate Catheter was positioned across the target lesion, the patient was randomized to treatment with either a placebo ribbon or Iridium-192 source ribbon. The dwell time for each individual patient was calculated based on the vessel diameter (as determined by intravascular ultrasound measurement), the number of seeds of the treatment ribbon and the activity of the treatment ribbon on the day of the procedure. This information is used by a radiation oncologist and physicist to determine the time required to deliver 800 cGy to the target farthest from the radiation source, with no more that 3000 cGy delivered to the target closet to the source.

Clinical Follow-up was completed at one, six and nine months; all patients underwent angiographic follow-up at 6 months. Baseline QCA was performed pre- and post-procedure. The baseline characteristics of the two patient populations in the GAMMA-I trial were similar. All treated patients were included in the intent-to-treat analysis. Antiplatelet therapy included aspirin 325 mg/daily (indefinitely) and ticlopidine 250 mg b.i.d for 8 weeks if a stent was implanted at the target lesion during the study procedure.

Results: In suitable patients with restenotic coronary lesions, an interventional procedure (IP) followed by intravascular brachytherapy (Radiation) resulted in a statistically significant improvement in late angiographic and intravascular ultrasound (IVUS) results, a lower six-month angiographic restenosis rate, and lower major adverse cardiac events (MACE) at 9 months when compared to IP and Placebo intravascular brachytherapy. The rate of late stent thrombosis was higher in the Radiation arm.

Clinical Trials Comparison

	GAMMA-I	SCRIPPS-I	WRIST	SCRIPPS-III	WRIST Plus
Trial	Pivotal Trial Multi center, prospective, randomized	Supportive Trial Single center, prospective, randomized	Supportive Trial Single center, prospective, randomized	Supportive Trial Multi center, registry	Supportive Trial Single center, registry
Total # of Patients Enrolled	252	60	130	500	120
Patients Studied	Native coronary arteries 2.75 - 4.0 mm diameter ≤ 45 mm length	Native coronary arteries and SVG's 3.0 – 5.5 mm diameter <30 mm length	Native coronary arteries and SVG's 3.0 – 5.0 mm diameter < 50 mm length	Native coronary arteries and SVG's 2.75 - 4.0 mm diameter < 81 mm length	Native coronary arteries and SVG's 2.5 – 5.0 mm diameter < 80 mm length
Devices Used	6, 10 or 14 seed ribbons 4F Catheter	5 or 9 seed ribbon 4F Catheter	5, 9 or 13 seed ribbon 5F Catheter	6 – 22 seed ribbons 4F Catheter	6-23 seed ribbons 4F or 5F Catheter
Methods	Outlined on previous page	Similar to GAMMA-1	Similar to GAMMA-I	Similar to GAMMA-I	Similar to GAMMA-I
Dosimetry	IVUS based 800-3000 cGy	IVUS based 800-3000 cGy	No IVUS 1500 cGy at 2 mm from the center of the source	No IVUS 1400 cGy at 2 mm	No IVUS 1400 cGy or 1500 cGy at 2 mm from the center of the source
Antiplatelet Therapy	8-weeks if new stent was placed	2 weeks if new stent was placed	4 weeks (all patients)	6 months if no new stent 12 months if new stent is placed	6 months (all patients)
Follow-up	6 months angiographic 1 & 9 months clinic 2, 24, 36 months telephone FU	6 & 36 months angiographic 12, 24, 36, 48, 60 months telephone FU	6 months angiographic 1, 6, 12 & 24 months clinic	1 & 9 months clinic 2 & 12 months telephone FU	6 & 24 months angiographic 1 & 12 months clinic

Table 8.1 GAMMA-I Principal Effectiveness and Safety Results (to 270 days)
All Patients Treated (N=252)

Effectiveness Measures	Radiation (N=131)	Placebo (N=121)	Relative Risk [95% CI]	Difference [95% CI]
Lesion Success	100.0% (131/131)	98.3% (119/121)	1.02 [0.99, 1.04]	1.7% [-0.6%, 3.9%]
Procedure Success	100.0% (131/131)	98.3% (119/121)	1.02 [0.99, 1.04]	1.7% [-0.6%, 3.9%]
Device Success	100.0% (131/131)	98.3% (119/121)	1.02 [0.99, 1.04]	1.7% [-0.6%, 3.9%]
Post Procedure In-Stent Percent Diameter Stenosis (% DS) Mean±SD (N)	8.8%±17.9% (129)	8.9%±19.0% (117)	N/A	-0.1% [-4.8%, 4.5%]
Range (min, max)	(-49.9%, 48.8%)	(-55.8%, 59.1%)		
Follow-Up In-Stent Percent Diameter Stenosis (% DS) Mean±SD(N)	33.6%±32.3% (111)	50.8%±22.0% (103)	N/A	-17.2% [-24.7%, -9.7%]
Range (min, max)	(-48.5%, 100.0%)	(-0.8%, 100.0%)		
In-Stent Late Loss (mm) Mean±SD (N)	0.73±0.79 (111)	1.14±0.65 (101)	N/A	-0.40 [-0.60, -0.20]
Range (min, max)	(-0.56, 3.37)	(-0.47, 3.30)		
6 Month In-Lesion (Stent+Probe+Edge) Binary Restenosis Rate	32.4% (36/111)	55.3% (57/103)	0.59 [0.43, 0.80]	-22.9% [-35.9%, -9.9%]
6 Month In-Stent Binary Restenosis Rate	21.6% (24/111)	50.5% (52/103)	0.43 [0.29, 0.62]	-28.9% [-41.2%, -16.5%]
Difference of Index and F/U Mean Difference of Stent and Lumen	-0.75±1.13 (35)	-1.55±1.15 (33)	N/A	0.80 [0.25, 1.35]
	(-3.80, 2.14)	(-4.48, 0.20)		
TLR-Free at 270 days*	74.8% [65.7%, 83.9%]	56.7% [46.1%, 67.3%]	1.32 [1.06, 1.65]	18.1% [4.1%, 32.1%]
TVR-Free at 270 days*	66.2% [56.3%, 76.1%]	52.5% [41.9%, 63.1%]	1.26 [0.98, 1.62]	13.8% [-0.7%, 28.2%]
TVF-Free at 270 days*	62.3% [52.1%, 72.5%]	51.6% [41.0%, 62.3%]	1.21 [0.93, 1.57]	10.7% [-4.1%, 25.4%]
MACE-Free at 270 days*	70.8% [61.2%, 80.4%]	55.0% [44.4%, 65.7%]	1.29 [1.02, 1.63]	15.8% [1.4%, 30.1%]
Safety Measures and Other Clinical Events				
In-Hospital MACE	2.3% (3/131)	3.3% (4/121)	0.69 [0.16, 3.01]	-1.0% [-5.1%, 3.1%]
Out-of-Hospital MACE to 270 days	26.7% (35/131)	42.1% (51/121)	0.63 [0.45, 0.90]	-15.4% [-27.0%, -3.8%]
Bleeding Complications to 270 days	2.3% (3/131)	0.8% (1/121)	2.77 [0.32, 23.91]	1.5% [-1.6%, 4.5%]
Vascular Complications to 270 days	3.1% (4/131)	1.7% (2/121)	1.85 [0.35, 9.66]	1.4% [-2.3%, 5.1%]
Hematologic Dyscrasia to 270 days	0.8% (1/131)	1.7% (2/121)	0.46 [0.04, 4.76]	-0.9% [-3.6%, 1.8%]
CVA to 270 days	0.8% (1/131)	2.5% (3/121)	0.31 [0.04, 2.58]	-1.7% [-4.9%, 1.4%]
Acute Stent Thrombosis	0.8% (1/131)	1.7% (2/121)	0.46 [0.04, 4.76]	-0.9% [-3.6%, 1.8%]
Late Thrombosis	5.3% (7/131)	0.8% (1/121)	6.47 [0.81, 51.79]	4.5% [0.3%, 8.7%]
Late Total Occlusion	12.6% (14/111)	5.8% (6/103)	2.17 [0.87, 5.42]	6.8% [-0.8%, 14.4%]

Numbers are % (counts/sample size) or Mean±SD — CI = Confidence Interval

Relative Risk = Radiation/Placebo — SE = sqrt $\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}$ — CI = RR* exp (± 1.96* SE)

Difference = Radiation – Placebo — SE = sqrt $(p_1*q_1/n_1+p_2*q_2/n_2)$ — CI = Diff ± 1.96* SE

N/A = Not Applicable

Lesion Success = Attainment of a <50% residual stenosis using any percutaneous method.

Procedure Success = Attainment of a <50% residual diameter stenosis using any percutaneous method and no in-hospital MACE.

Device Success = Attainment of a <50% residual stenosis and successful delivery of the radiation device.

Restenosis was defined as ≥50% in-stent diameter stenosis at the follow-up angiogram.

*Survival Estimates from Kaplan-Meier estimate. Standard Error estimates by Peto formula.

KM Relative Risk = $S_{Radiation}/S_{Placebo}$ — $SE_{RR}=sqrt\{(SE_{Radiation}/S_{Radiation})^2+(SE_{Placebo}/S_{Placebo})^2\}$ — $CI = RR*exp(\pm 1.96*SE_{RR})$

KM Difference = $S_{Radiation} - S_{Placebo}$ — $SE_{Diff} = sqrt(SE_{Radiation}^2+SE_{Placebo}^2)$ — $CI = Diff \pm 1.96*SE_{Diff}$

TLR-Free = No target lesion revascularization.

TVR-Free = No target vessel revascularization.

TVF-Free = No death, MI, or target lesion revascularization.

MACE-Free = No death, Q wave or non-Q wave MI, emergent CABG, or target lesion revascularization.

MACE = Death, Q wave or non-Q wave MI, emergent CABG, or target lesion revascularization.

In-Hospital MACE = Death, Q wave or non-Q wave MI, emergent CABG, or target lesion revascularization prior to hospital discharge.

Out-of-Hospital MACE = Death, Q wave or non-Q wave MI, emergent CABG, or target lesion revascularization after hospital discharge.

Bleeding Complications = Transfusions of blood products due to blood loss resulting from the percutaneous revascularization procedure.

Vascular Complications = Hematoma > 4 cm, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, and vascular surgical repair.

CVA = Acute neurological deficits recorded by the clinical sites that persisted > 24 hours.

Acute Stent Thrombosis = Angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven angiographic restudy for documented ischemia (chest pain or ECG changes). Any death not attributed to a non-cardiac cause within the first 30 days was considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

Late Thrombosis = Myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and in a newly implanted bypass graft at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.

Late Total Occlusion = Consists of Late Thrombosis and Total Occlusion.

Table 8.2 SCRIPPS-I Principal Effectiveness and Safety Results (to 180 days)
All Patients Treated (N=60)

Effectiveness Measures	Radiation (N=29)	Placebo (N=31)	Relative Risk [95% CI]	Difference [95% CI]
Lesion Success	100.0% (29/29)	93.5% (29/31)	1.07 [0.97, 1.18]	6.5% [-2.2%, 15.1%]
Procedure Success	100.0% (29/29)	93.5% (29/31)	1.07 [0.97, 1.18]	6.5% [-2.2%, 15.1%]
Device Success	100.0% (29/29)	90.3% (28/31)	1.11 [0.98, 1.24]	9.7% [-0.7%, 20.1%]
Post Procedure In-Stent Percent Diameter Stenosis (% DS)				
Mean±SD (N)	9.4±22.8% (29)	7.0%±23.9% (31)	N/A	2.5% [-9.6, 14.5]
Range (min, max)	(-64.1%, 38.0%)	(-36.0%, 46.4%)		
Post-Procedure In-Stent+Border % DS				
Mean±SD(N)	24.4%±9.5% (29)	18.9±18.1% (31)	N/A	5.6% [-2.0%, 13.1%]
Range (min, max)	(-0.8%, 39.8%)	(-24.3%, 53.2%)		
6 Month F/U In-Stent+Border % DS				
Mean±SD (N)	43.2%±23.5% (28)	41.8%±24.2% (28)	N/A	1.4% [-11.4%,14.2%]
Range (min, max)	(16.5%, 100%)	(-23.8%, 78.6%)		
6 Month F/U In-Stent+Border Late Loss				
Mean±SD (N)	0.66±0.91 (28)	0.78±0.94 (28)	N/A	-0.13 [-0.62, 0.37]
Range (min, max)	(-0.62, 2.73)	(-0.46, 3.49)		
6 Month In-Stent+Border Restenosis Rate	21.4% (6/28)	46.4% (13/28)	0.46 [0.21, 1.00]	-25.0% [-48.9%, -1.1%]
Difference between Post-Procedure and 6-Month F/U Mean Intimal Hyperplasia CSA (mm^2)				
Mean±SD (N)	-0.68±0.97 (18)	-2.14±1.66 (18)	N/A	1.47 [0.55, 2.39]
Range (min, max)	(-2.90, 0.70)	(-5.60, -0.40)		
TLR-Free at 180 days*	82.6% [68.5%, 96.7%]	77.4% [62.4%, 92.5%]	1.07 [0.82, 1.38]	5.2% [-15.4%, 25.8%]
TVR-Free at 180 days*	82.8% [68.7%, 96.8%]	71.0% [54.6%, 87.3%]	1.17 [0.88, 1.55]	11.8% [-9.8%, 33.3%]
TVF-Free at 180 days*	79.3% [64.2%, 94.4%]	71.0% [54.6%, 87.3%]	1.12 [0.83, 1.51]	8.3% [-13.9%, 30.6%]
MACE-Free at 180 days*	79.2% [64.1%, 94.3%]	77.4% [62.4%, 92.5%]	1.02 [0.78, 1.34]	1.7% [-19.6%, 23.1%]
Safety Measures and Other Clinical Events				
In-Hospital MACE	0.0% (0/29)	0.0% (0/31)	- [-,-]	0.0% [-,-]
Out-of-Hospital MACE to 180 days	20.7% (6/29)	22.6% (7/31)	0.92 [0.35, 2.42]	-1.9% [-22.7%, 18.9%]
Bleeding Complications to 180 days	0.0% (0/29)	6.5% (2/31)	0.00 [-,-]	-6.5 [-15.1%, 2.2%]
Vascular Complications to 180 days	0.0% (0/29)	0.0% (0/31)	- [-,-]	0.0% [-,-]
CVA to 180 days	0.0% (0/29)	3.2% (1/31)	1.00 [-, -]	-3.2% [-9.4%, 3.0%]
Acute Stent Thrombosis	3.4% (1/29)	0.0% (0/31)	- [-,-]	3.4% [-3.2%, 10.1%]
Late Thrombosis	0.0% (0/29)	0.0% (0/31)	- [-,-]	0.0% [-,-]
Late Total Occlusion	3.6% (1/28)	0.0% (0/28)	- [-,-]	3.6% [-3.3%, 10.5%]

Numbers are % (counts/sample size) or Mean ± SD — CI = Confidence Interval

Relative Risk = Radiation/Placebo — SE = sqrt $\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}$ — CI = RR* exp (± 1.96* SE)

Difference = Radiation – Placebo — SE = sqrt $(p_1*q_1/n_1+p_2*q_2/n_2)$ — CI = Diff ± 1.96* SE

N/A = Not applicable.

Device Success = The attainment of a <50% residual stenosis and successful delivery of the radiation device.

Lesion Success = The attainment of a <50% residual stenosis using any percutaneous method.

Procedure Success = The attainment of a <50% residual stenosis using any percutaneous method and no in-hospital MACE.

In-Hospital MACE = Death, Q wave or non-Q wave MI, target lesion revascularization, and emergent CABG prior to hospital discharge.

Out-of-Hospital MACE = Death, Q wave or non-Q wave MI, target lesion revascularization, and emergent CABG after hospital discharge.

*Survival Estimates from Kaplan-Meier estimates. Standard Error estimates from Peto formula.

KM Relative Risk = $S_{Radiation}/S_{Placebo}$ — $SE_{RR}=sqrt\{(SE_{Radiation}/S_{Radiation})^2+(SE_{Placebo}/S_{Placebo})^2\}$ — $CI = RR*exp(\pm 1.96*SE_{RR})$

KM Difference = $S_{Radiation} - S_{Placebo}$ — $SE_{Diff} = sqrt\{SE_{Radiation}^2+SE_{Placebo}^2\}$ — $CI = Diff \pm 1.96*SE_{Diff}$

TLR-Free = No target lesion revascularization.

TVR-Free = No target vessel revascularization.

TVF-Free = No death, Q wave or non-Q wave MI, or target vessel revascularization.

MACE-Free = No death, Q wave or non-Q wave MI, target lesion revascularization, or emergent CABG.

Bleeding Complications = Bleeding complications were defined as transfusions of blood products due to blood loss resulting from the percutaneous revascularization procedure.

Vascular Complications = Hematoma > 4 cm, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, and Vascular surgical repair.

CVA = Cerebrovascular accident was defined as acute neurological deficits recorded by the clinical sites that persisted > 24 hours.

Acute Stent Thrombosis = Angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven angiographic restudy for documented ischemia (chest pain or ECG changes). Any death not attributed to a non-cardiac cause within the first 30 days was considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

Late Thrombosis = Myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and in a newly implanted bypass graft at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.

Late Total Occlusion = Consists of Late Thrombosis and Total Occlusion.

Table 8.3 WRIST Principal Effectiveness and Safety Results (to 180 days +/- 30 days) All Patients Treated (N=130)

Effectiveness Measures	Radiation (65=Patients, 65=Lesions)	Placebo (65=Patients, 65=Lesions)	Relative Risk (95% CI)	Difference (95% CI)
Lesion Success	100% (64/64)	98.4% (63/64)	1.02 (0.99, 1.05)	1.6 (-1.5, 4.7)
Device Success	100% (64/64)	96.9% (62/64)	1.03 (0.99, 1.08)	3.1 (-1.2, 7.5)
Procedure Success	100% (64/64)	98.4% (63/64)	1.02 (0.99, 1.05)	1.6 (-1.5, 4.7]
Post-Procedure In-Lesion Percent Diameter Stenosis (% DS) Mean±SD (N)	28.32±11.93 (64)	27.30±11.99 (64)	N/A	1.02 (-3.16, 5.20)
Range (min, max)	(-10.07, 63.21)	(2.29, 55.88)		
Post Procedure In-Stent Percent Diameter Stenosis (% DS) Means±SD (N)	19.77±15.16 (64)	20.45±14.75 (64)	N/A	-0.68 (-5.91, 4.56)
Range (min, max)	(-18.80, 43.01)	(-20.23, 50.46)		
Late Loss In-Stent (QCA) Mean±SD (N)	0.24±0.84 (59)	0.96±-0.68 (55)	N/A	-0.72 (-1.01, -0.44)
Range (min, max)	(-1.20, 2.95)	(-0.82, 2.62)		
Restenosis Rate In-Lesion Binary Restenosis	23.7% (14/59)	60.7% (34/56)	0.39 (0.24, 0.65)	-37.0 (-54.1, -19.9)
Mean Lumen Area at 6 month follow-up (IVUS) Means±SD (N)	7.04±2.38 (47)	4.85±2.88 (50)	N/A	(1.12, 3.26)
TLR-free at 6 months	84.6% (55/65)	36.9% (24/65)	2.29 (1.64, 3.20)	47.7 (32.8, 62.6)
TVR-free at 6 months	72.3% (47/65)	32.3% (21/65)	2.24 (1.53, 3.28)	40.0 (24.0, 56.0)
MACE-free at 6 months	70.8% (46/65)	32.3% (21/65)	2.19 (1.49, 3.22)	38.5 (22.3, 54.6)
Safety Measures				
In-Hospital MACE	1.5% (1/65)	0.0% (0/65)	3.00 (0.12, 72.31)	1.5 (-1.5, 4.6)
Out-of-Hospital MACE to 6 months	29.2% (19/65)	67.7% (44/65)	0.43 (0.29, 0.65)	-38.5 (-54.6, -22.3)
MACE to 30 days (cumulative)	3.1% (2/65)	1.5% (1/65)	2.00 (0.19, 21.52)	1.5 (-3.7, 6.8)
MACE to 6 months (cumulative)	29.2% (19/65)	67.7% (44/65)	0.43 (0.29, 0.65)	-38.5 (-54.6, -22.3)
Abrupt Closure to 30 days	0.0% (0/65)	0.0% (0/65)		
Subacute Closure to 30 days	0.0% (0/65)	0.0% (0/65)		
Stent Thrombosis to 30 days	0.0% (0/65)	0.0% (0/65)		
CVA to 30 days	0.0% (0/65)	0.0% (0/65)		
In-hospital Vascular Complications	10.8% (7/65)	10.8% (7/65)	1.00 (0.37, 2.69)	0.0 (-10.8, 10.8)
Vascular Complications to 6 months (cumulative)	12.3% (8/65)	12.3% (8/65)	(0.40, 2.50)	0.0 (-11.5, 11.5)
Late Thrombosis	3.1% (2/65)	0.0% (0/65)		3.1 (-1.1, 7.3)
Late Total Occlusion	13.8% (9/59)	1.5% (1/56)*	9.00 (1.17, 69.02)	12.3 (3.4, 21.2)

Numbers are % (counts/sample size) or Mean ± SD — CI = Confidence Interval

Relative Risk = p_1/p_2, $p_i = n_{i1}/n_i$ — SE = sqrt $\{(1-p_1/n_{11}+(1-p_2)/n_{21})\}$ — CI = RR*exp (± 1.96* SE)

Difference = p_1-p_2 — SE = sqrt $\{(p_1*q_1/n_1+p_2*q_2/n_2)\}$ — CI = Diff ± 1.96* SE

N/A = Not applicable

Lesion success = Lesion success was defined as the attainment of <50% residual stenosis (by QCA) using percutaneous method.

Device Success = Device success was defined as the attainment of a <50% residual stenosis using assigned treatment and delivery of the ribbon for the desired dwell time.

Procedure Success = Procedure success was defined as the attainment of a <50% residual stenosis by QCA and freedom from death, Q wave MI or emergent CABG.

Post-Procedure In-Lesion Percent Diameter Stenosis (% DS) = The % diameter stenosis post procedure was defined as (1-MLD/RVD) *100 as is identified within the stenotic segment ("in lesion"). Whenever possible, normal and minimal lesion diameters are calculated from two "orthogonal" projections. Range (min, max) measurement of smallest stenosis and largest stenosis, respectively.

Post Procedure In-Stent Percent Diameter Stenosis (% DS) = The stent % diameter stenosis post procedure was defined as (1-MLD-RVD) * 100 as is identified within the stent ("in stent"). Whenever possible, normal and minimal lesion diameters are calculated from two "orthogonal" projections. Range (min, max) measurement of smallest stenosis and largest stenosis, respectively.

Late Loss = Late loss is defined as the late change in dimensional minimal lumen diameter that occurred during the follow-up period measured by quantitative coronary angiography based on the average from two orthogonal views after the final post-dilatation to follow-up. Final MLD – FU MLD. Reported for in-stent.

Binary Restenosis = Angiographic restenosis ≥ 50% minimum lumen diameter stenosis at the follow-up angiogram. Restenosis is recorded for in lesion.

Mean Lumen Area = Average lumen area over the length of treated segment as measured by intravascular ultrasound at 6 months follow-up in mm^2.

TLR-free at 6 months = Target lesion revascularization was defined as a clinically driven repeat revascularization of a target lesion that was angiographically narrowed. The definition of "clinically driven" included a positive functional ischemia study, resting ischemic ECG changes in a distribution consistent with the target vessel, ischemic symptoms, and angiographic minimal lumen diameter stenosis ≥ 50% by QCA; revascularization of a target lesion with diameter stenosis ≥ 70% by QCA without either angina or a positive functional study was also considered clinically driven.

Cd

Table 8.3 Continued

TVR-free at 6 months = Target vessel revascularization was defined as a target lesion revascularization (defined above) or revascularization due to narrowing of any segment of the target vessel proximal or distal to the target lesion. This definition assumed that the entire vessel was vulnerable to late failure because of guide catheter or guidewire trauma or progression of disease remote from the treatment site. The target vessel revascularization definition required that: target vessel revascularization was clinically driven (as defined for the target lesion revascularization, see above). The angiographic core laboratory determined that the target lesion had a diameter stenosis of $\geq$ 50% by QCA or the clinical site reported a narrowing of another site in the target vessel with diameter stenosis $\geq$ 50%.

MACE-free at 6 months = MACE was defined as target vessel revascularization, Q wave myocardial infarction or cardiac death that could not be clearly attributed to a non-target vessel. Therefore, target vessel failure included any revascularization or adverse endpoints due to renarrowing of any segment of the target vessel. Target vessel failure was reported when: target vessel revascularization occurred (defined below); myocardial infarction occurred and the territory was not clearly other than that of the target vessel; or cardiac death occurred and could not be clearly attributed to a non-target vessel.

In-Hospital MACE = In-hospital MACE (Major Adverse Cardiac Events) were defined as cardiac death, target Q wave MI, and target *vessel* revascularization (CABG or PTCA of the target vessel) as determined by the independent Clinical Events Committee from index procedure through the hospital discharge.

Out-of-Hospital MACE = Out-of-hospital MACE (Major Adverse Cardiac Events) were defined as death, Q wave MI, and target vessel revascularization (CABG or PTCA of the target vessel) as determined by the independent Clinical Events Committee from discharge through the 6 month contact.

MACE to 30 days (cumulative) = The occurrence of any major adverse cardiac event including cardiac death, QWMI, CABG, or repeat PTCA within 30 days of the index procedure. One event should be reported per patient.

MACE to 6 months (cumulative) = The occurrence of any major adverse cardiac event including cardiac death, QWMI and target vessel revascularization that occurred from the index procedure to the 6 month follow-up. One event should be reported per patient.

Abrupt Closure = Abrupt closure is defined as the occurrence of new reduced flow (TIMI 0 or 1) of the target vessel and required rescue by another device or emergency surgery or resulted in myocardial infarction or death. Abrupt closure is related to the mechanical dissection (of the treatment site or other instrumental site), coronary thrombus, or severe spasm. Abrupt closure does not connote no re-flow in which the artery was patent but reduced flow persisted. Abrupt closure also does not connote transient closure unless a Class 2 or 3 MI or death occurred. Threatened abrupt closure was defined as a NHLBI dissection Grade B with a 50% diameter stenosis or any Grade C dissection or higher. Threatened closure was not used as a primary endpoint but was used to adjudicate the use of other devices.

Subacute Closure to 30 days = Subacute closure was defined as abrupt closure that had occurred after the index procedure was completed and the patient had left the catherization laboratory and was within 30 days of the index procedure.

Stent Thrombosis = Cardiac death, Q wave MI, angiographic total occlusion at follow-up or evidence of angiographic thrombus (core laboratory and investigator), reported at 30 days. In the absence of the QCA, total occlusion was adjudicated by the Clinical Events Committee.

CVA to 30 days = The occurrence of a new permanent stroke following the procedure within 30 days of the index procedure.

In-Hospital Vascular Complications = In-hospital vascular complications were defined as the occurrence of any of the following: hematoma at the access site of > 4 cm in maximum diameter, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, procedure-related blood transfusion, or vascular surgical repair between index procedure to discharge date of hospital stay.

Vascular Complications to 6 months (cumulative) = Vascular complications were defined as the occurrence of any of the following: hematoma at the access site of > 4 cm in maximum diameter, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, procedure related blood transfusion, or vascular surgical repair both in hospital from index procedure to discharge and out of hospital.

Late Thrombosis = Myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and in a newly implanted bypass graft at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.

Late Total Occlusion = Consists of Late Thrombosis and Total Occlusion.

* Additionally, the rates of late thrombosis and late total occlusion for the crossover groups are 5.1% (2/39) and 12.8% (5/39), respectively.

Table 8.4: Major Adverse Cardiac Events – In-Hospital vs. Out-of-Hospital
All Patients Treated

	GAMMA-I			SCRIPPS-I			WRIST		
	Radiation (N=131)	Placebo (N=121)	All (N=252)	Radiation (N=29)	Placebo (N=31)	All (N=60)	Radiation (N=65)	Placebo (N=65)	All (N=130)
In-Hospital Complications									
MACE (Death, MI, Emergent CABG, TLR)*	2.3% (3)	3.3% (4)	2.8% (7)	0.0% (0)	0.0% (0)	0.0% (0)	1.5% (1)	0.0% (0)	0.8% (1)
Death (for WRIST: non-cardiac death only)	0.8% (1)	0.0% (0)	0.4% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Myocardial Infarction (Q or Non-Q)	2.3% (3)	2.5% (3)	2.4% (6)	0.0% (0)	0.0% (0)	0.0% (0)	10.8% (7)	7.7% (5)	9.2% (12)
Q Wave MI	0.8% (1)	0.8% (1)	0.8% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Non-Q Wave MI	1.5% (2)	1.7% (2)	1.6% (4)	0.0% (0)	0.0% (0)	0.0% (0)	10.8% (7)	7.7% (5)	9.2% (12)
Emergent CABG	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Target Lesion Revascularization	0.0% (0)	1.7% (2)	0.8% (2)	0.0% (0)	0.0% (0)	0.0% (0)	1.5% (1)	0.0% (0)	0.8% (1)
TL-CABG	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
TL-PTCA	0.0% (0)	1.7% (2)	0.8% (2)	0.0% (0)	0.0% (0)	0.0% (0)	1.5% (1)	0.0% (0)	0.8% (1)
Perforation	0.8% (1)	0.0% (0)	0.4% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Bleeding Complications	0.8% (1)	0.0% (0)	0.4% (1)	0.0% (0)	6.5% (2)	3.3% (2)	6.2% (4)	1.5% (1)	3.8% (5)
Vascular Complications	2.3% (3)	0.8% (1)	1.6% (4)	0.0% (0)	0.0% (0)	0.0% (0)	10.8% (7)	10.8% (7)	10.8% (14)
Hematologic Dyscrasia	0.0% (0)	0.0% (0)	0.0% (0)	N/A	N/A	N/A	N/A	N/A	N/A
CVA	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Acute Stent Thrombosis (to 30 days)	0.0% (0)	0.8% (1)	0.4% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Late Thrombosis	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	N/A	N/A	N/A
Late Total Occlusion	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	N/A	N/A	N/A
Out-of-Hospital Complications**									
MACE (Death, MI, Emergent CABG, TLR)	26.7% (35)	42.1% (51)	34.1% (86)	20.7% (6)	22.6% (7)	21.7% (13)	29.2% (19)	67.7% (44)	48.5% (63)
Death	2.3% (3)	0.8% (1)	1.6% (4)	0.0% (0)	0.0% (0)	0.0% (0)	4.6% (3)	6.2% (4)	5.4% (7)
Myocardial Infarction (Q or Non-Q)	9.9% (13)	4.1% (5)	7.1% (18)	6.9% (2)	3.2% (1)	5.0% (3)	9.2% (6)	7.7% (5)	8.5% (11)
Q Wave MI	4.6% (6)	2.5% (3)	3.6% (9)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Non-Q Wave MI	5.3% (7)	1.7% (2)	3.6% (9)	6.9% (2)	3.2% (1)	5.0% (3)	9.2% (6)	7.7% (5)	8.5% (11)
Emergent CABG	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	N/A	N/A	N/A
Target Lesion Revascularization	24.4% (32)	40.5% (49)	32.1% (81)	17.2% (5)	22.6% (7)	20.0% (12)	15.4% (10)	63.1% (41)	39.2% (51)
TL-CABG	9.9% (13)	20.7% (25)	15.1% (38)	3.4% (1)	3.2% (1)	3.3% (2)	7.7% (5)	6.2% (4)	6.9% (9)
TL-PTCA	19.8% (26)	25.6% (31)	22.6% (57)	13.8% (4)	19.4% (6)	16.7% (10)	9.2% (6)	61.5% (40)	35.4% (46)
Perforation	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Bleeding Complications	1.5% (2)	0.8% (1)	1.2% (3)	0.0% (0)	0.0% (0)	0.0% (0)	N/A	N/A	N/A
Vascular Complications	0.8% (1)	0.8% (1)	0.8% (2)	0.0% (0)	0.0% (0)	0.0% (0)	3.1% (2)	3.1% (2)	3.1% (4)
Hematologic Dyscrasia	0.8% (1)	1.7% (2)	1.2% (3)	NA	NA	NA	N/A	N/A	N/A
CVA	0.8% (1)	2.5% (3)	1.6% (4)	0.0% (0)	3.2% (1)	1.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Acute Stent Thrombosis (to 30 days)	0.8% (1)	0.8% (1)	0.8% (2)	3.4% (1)	0.0% (0)	1.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Late Thrombosis	5.3% (7)	0.8% (1)	3.2% (8)	0.0% (0)	0.0% (0)	0.0% (0)	3.1% (2)	0.0% (0)	1.5% (2)
Late Total Occlusion***	12.6% (14)	5.8% (6)	9.3% (20)	3.6% (1)	0.0% (0)	1.7% (1)	13.8% (9)	1.5% (1)	7.7% (10)

* MACE for GAMMA-I and SCRIPPS-I = Death, MI (Q Wave and non-Q Wave), Emergency CABG and TLR)
MACE for WRIST = Cardiac death, Q Wave MI, Emergency CABG and TVR.
** Out of Hospital Complications: GAMMA-I: to 270 days
SCRIPPS-I: to 180 days
WRIST: 180 days +/- 30 days
***Based on follow-up angiogram.

8.1 Additional Late Thrombosis Information

Summarized in Table 8.5 is the late thrombosis information based on data collected from the GAMMA-I, SCRIPPS-I and WRIST trials up to June 2000, which is beyond the primary study endpoints (See Table 8.5 for further details).

Table 7.5: Late Thrombosis GAMMA-I, SCRIPPS-I, WRIST*

	Radiation	Placebo
GAMMA-I	5.3% (7/131)	0.8% (1/121)
SCRIPPS-I	0.0% (0/29)	0.0% (0/31)
WRIST	6.2% (4/65)	1.5% (1/65)
WRIST (Crossover)	5.1% (2/39)	–
TOTAL	**4.9% (13/264)**	**0.9% (2/217)**

GAMMA-I: Results in this table represent data at 1.5 years. Patients with new stents received 8 weeks of antiplatelet therapy.
SCRIPPS-I: Results in this table represent data at 3 years. Patients with new stent received 2 weeks of antiplatelet therapy.
WRIST: Results in this table represent data at 2 years. All patients received 4 weeks of antiplatelet therapy.
Late Thrombosis = Myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and in a newly implanted bypass graft at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.

Additionally, the use of prolonged antiplatelet therapy was evaluated during the SCRIPPS-III and WRIST Plus registry trials. During the SCRIPPS-III trial, patients who received a new stent are placed on 12 months of antiplatelet medication and 6 months if no new stent is placed. During the WRIST Plus trial all patients received 6 months of antiplatelet medication. A summary of late thrombosis events up to August 18, 2000 can be found in Table 8.6. Note: The follow-up in these two trials is not yet complete, since the studies are still on-going.

Table 8.6
Survival Free From Late Thrombosis: SCRIPPS-III, WRIST Plus trials
Event-Free Survival; All Patients Treated (n=534)

Time After Initial Procedure (days)	0	30	60	90	120	150	180	210
Effective Sample Size	508.5	481.5	447.5	413.5	379.0 *	333.5	269.5	206.0
Number Censored	19	35	31	35	34	57	71	54
Number of Events	0	1	1	0	0	0	1	0
% Survival	100%	100%	99.79%	99.56%	99.56%	99.56%	99.56%	99.17%
% Failure	0.00%	0.00%	0.21%	0.44%	0.44%	0.44%	0.44%	0.83%
% Peto Survival SE	0.00%	0.00%	0.21%	0.32%	0.33%	0.35%	0.38%	0.57%
% Failure 95% Lower Conf. Limit	0.00%	0.00%	0.03%	0.10%	0.10%	0.09%	0.08%	0.22%
% Failure 95% Upper Conf. Limit	0.00%	0.00%	1.53%	1.81%	1.92%	2.05%	2.36%	3.18%

9. Patient Selection and Treatment

9.1 Individualization of Treatment

The risks and benefits described above should be carefully considered for each patient before use of intravascular brachytherapy. Patient selection factors to be assessed should include a judgement regarding risk of prolonged anticoagulation. Intravascular brachytherapy with stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease, see CONTRAINDICATIONS).

Premorbid conditions that increase the risk of a poor initial result and the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed. The relation of baseline and procedural variables to Major Adverse Cardiac Events (MACE) was examined. The only significant univariate predictors of MACE in the GAMMA-I trial were lesion length and post-procedural mean in-stent minimum lumen diameter (MLD). MACE was more likely with longer lesions and smaller MLD.

9.2 Use in Special Populations

The safety and effectiveness of the Cordis Checkmate System has not been established because it has not been adequately studied in:

- Patients with coronary artery **reference vessel diameter < 2.75 mm and > 4.0 mm.**
- Patients with target **lesions longer than 45 mm.**
- Patients with **vascular disease other than in-stent** coronary artery stenosis.
- Patients with recent **acute myocardial infarction** and there is evidence of thrombus.
- Patients with **lesions located** in the left main coronary artery, saphenous vein grafts or internal mammary arteries.

10. Patient Counseling Information

Physicians should consider the following in counseling the patient about this device:

- Discuss the risks associated with exposure to radiation.
- Discuss the risk/benefit issues for this particular patient.
- Discuss alterations to current lifestyle immediately following the procedure and over the long term.

11. How Supplied

STERILITY. The Ir-192 source ribbon and delivery device **ARE NOT STERILE.** Do not autoclave the Ir-192 source ribbon and delivery device. Exposure to temperatures above 54°C (130°F) and pressures in excess of 15 psi (103.4 kPa) may damage the components.
CONTENTS. One (1) Ir-192 source ribbon and one (1) Checkmate Delivery Device.

STORAGE. When not in use, the Ir-192 source ribbon and delivery device should be stored in a secure, locked area with restricted access separate from other medical devices. Radiation safety regulations for storage of radioactive material should be strictly adhered to. Store in a cool, dry, dark place.

Table 11.1
Device Specification

	Ir-192 Source Ribbon	Delivery Device
Device Specifications	Overall Length: 230.0 cm Ribbon O.D.: 0.030" Treatment Length: 6-seed: 23 mm 10-seed: 39 mm 14-seed: 55 mm Ribbon Color: clear Filament Color: 6-seed: blue 10-seed: green 14-seed: purple	
Compatible With	Cordis Checkmate Catheter	Cordis Checkmate Catheter

12. Operator Manual

12.1 Materials Required

The following materials are required to perform a Checkmate intravascular brachytherapy procedure after a successful revascularization procedure has been performed:

Quantity	Material
	Appropriate guiding catheter(s) (See Table 11.1, Device Specification)
1	Guidewire (See Table 11.1, Device Specification)
1	Cordis Checkmate Catheter (with dummy ribbon)
1	Rotating luer connector
As required	Portable lead shield(s)
As required	Radiation detection equipment

12.2 Preparation and Inspection

Warnings

- Avoid performing the intervention and/or injuring a vessel segment outside of the radiation treatment area.

Precautions

- **For multiple uses.** Do not sterilize.
- Do NOT use after the "Use By" date as the function may be compromised.
- Carefully inspect the package before opening. If the package is damaged, the contents may be damaged as well.
- If radioactivity readings register above the acceptable range, notify the institutional radiation safety officer immediately and follow the established institutional radiation safety protocol.
- Until ready for use, the transport cart carrying the shielded delivery device with the radioactive source ribbon should remain in a secure, locked location with restricted access separate from other medical devices.

12.2.1 Checkmate Delivery Device

Step	Action
1	Upon receipt at the institution, inspect the shipping/storage container of the shielded delivery device. Using a calibrated survey meter, survey the exterior of shipping/storage container to verify that the radioactivity level is within the acceptable range as defined by the standards established by the governing nuclear regulatory agency.
2	Open the shipping container, carefully remove the shielded delivery device (two person lift) and place on a sturdy transport cart. NOTE: The shielded delivery device is heavy. Retain the shipping container for return shipping , see "Return Shipping Guidelines".
3	Survey the outside surface of the shielded delivery device with a calibrated survey meter. NOTE: It is recommended that survey readings are made throughout the procedure to ensure that radioactivity remains within an acceptable level.
4	Verify the "Use By" date of the radioactive source ribbon from the labeling. Do not use a source ribbon after the "Use By" date.

12.2.2 Source Calibration

Precautions:

- If radioactivity readings register above the acceptable range, notify the institutional radiation safety officer immediately and follow the established institutional radiation safety protocol.
- Do NOT use the source ribbon if the specific activity is above the site license limit for the procedure room.
- Do NOT use the source ribbon if kinks are detected. Return the source ribbon per the "Return Shipping Guidelines".

Step	Action
1	Remove the metal caps from both ends of the shielded delivery device. Uncoil the ribbon from the spool (proximal end of the shielded delivery device).
2	Remove the threaded cap at the distal end of the shielded delivery device. Open the fitting at the proximal end of the delivery device and advance the source ribbon by pushing it from the proximal end. Verify the activity of the Ir-192 source ribbon per the site (incoming) calibration procedure. - it is recommended to standardize the calibrator using an ADCL or NIST traceable Ir-192 seed. - it is recommended to verify the linearity and geometry variation of the calibrator that is used. NOTE: The air kerma strength conversion factor is 4.030 U mCi^{-1} (AAPM TG-43).
3	Verify by using calibrated instruments, that the activity of the Ir-192 source ribbon matches that listed on the Calibration Certificate (or Bill of Lading) and verify that the number of seeds matches the product labeling. The activity information will be used to calculate dosimetry.
4	Notify the manufacturer if there are any discrepancies between the measured and labeled activity and the number of seeds of the Ir-192 source ribbon.
5	Withdraw the source ribbon into the shielded delivery device. Use the visual markers on the source ribbon and a survey meter to ensure that the source ribbon is correctly positioned within the delivery device. Secure the source ribbon by tightening the fitting on the proximal end of the delivery device. Place the threaded cap over the exit port on the distal end of the delivery device.
6	Inspect the proximal length of the source ribbons protruding from the delivery device. Verify that there are no kinks in the ribbon that may impede advancement through the catheter. Recoil the ribbon as needed.

12.2.3 Checkmate Catheter, Dummy Ribbon and Source Lumen Plug

Step	Action
1	Follow the instructions provided with the Cordis Checkmate Catheter for procedures associated with preparing the Checkmate Catheter, dummy ribbon and source lumen plug.

12.3 Recommended Procedure (See also the Instructions for Use of the Checkmate Catheter.)

12.3.1 Treatment Prerequisite

Step	Action
1	Perform revascularization of the previously stented target lesion using current interventional techniques. NOTE: Refer to "System Compatibility" section for catheter size and compatibility information.
2	Verify satisfactory result with angiography and/or IVUS. NOTE: It is important that an optimal redilatation of the restenotic lesion is achieved prior to intravascular brachytherapy.
3	Maintain the position of the procedure guidewire across the target lesion.

12.3.2 Dosimetry

Warnings:

- The biological risks of doses above 3000 cGy to the near wall have not been established.

Step	Action
1	Using intravascular ultrasound (IVUS), measure the distance from the center of the IVUS catheter to the leading edge of the tunica media. Measure a minimum of three (3) sites along the stent vessel segment.
2	Determine the maximum and minimum source to target distances along the stented vessel.
3	Calculate the dwell time to deliver the desired dose by using the maximum and minimum source to target distances and the specific activity level of the Ir-192 source from the Certificate of Activity (Bill of Lading) supplied with the Checkmate Delivery System, see also the Radiation Therapy Worksheet , Attachment 1. • The dwell time should be calculated such that a dose of 800 cGy is delivered to the target farthest from the radiation source provided that no more than 3000 cGy is delivered to the target closest to the radiation source. • If the dose to the near wall is calculated to be more than 3000 cGy, the dwell time should be based on delivering 3000 cGy to the near wall. In this case, calculate and use the dose to be delivered to the far wall.
4	Document the dose calculations.

12.3.3 Checkmate Catheter Introduction and Positioning

Precautions:

- Care should be taken when inserting the Checkmate Catheter into the hemostasis valve and during tightening of the hemostasis valve in order to avoid crimping or kinking of the catheter.
- DO NOT advance the Checkmate Catheter within the vasculature unless it is preceded by a guidewire. The catheter can disengage from the guidewire if it is pushed past the guidewire tip. If this occurs, remove the catheter while leaving the guidewire in place and repeat steps 2-4 for catheter introduction.
- DO NOT advance the catheter over the floppy portion of the guidewire as the guidewire may prolapse when the catheter is withdrawn. If this occurs, attempt to resolve the prolapse by gently pulling back on the guidewire while simultaneously advancing the catheter. If the prolapse persists, disengage the catheter from the guidewire by continuing to advance the catheter while gently pulling back on the guidewire. Remove the catheter (or the catheter and guidewire as a unit).
- DO NOT flush the source lumen with saline or other liquids. If the source lumen gets wet, remove the Checkmate Catheter and discard.

Step	Action
1	Attach a hemostasis valve to the luer port of the guiding catheter positioned in the vasculature.
2	Under fluoroscopy, verify that the procedure guidewire is correctly positioned across the target lesion.
3	Protect the proximal end of the Checkmate Catheter from blood or fluid contact.
4	Insert the proximal end of the indwelling guidewire into the distal end of the Checkmate Catheter. The guidewire will exit through the port on the catheter tip. NOTE: Before inserting the Checkmate Catheter, wipe the proximal end of the guidewire with a saline soaked gauze to remove any excess contrast medium.
5	Under fluoroscopy, advance the Checkmate Catheter over the guidewire. Position the catheter across the target lesion using the radiopaque markers on the catheter and dummy ribbon to define the target lesion. NOTE: It is recommended that the treatment zone includes a margin of approximately 3-5 mm (1-1.33 seeds) on either side of the target lesion (see illustration). NOTE: Care should be taken to avoid rotating the Checkmate Catheter as it is advanced over the guidewire. Such action may cause the guidewire to wrap around the catheter making further advancement difficult.
6	Make any adjustments to the catheter position when the dummy ribbon is in place. When satisfied that the catheter is correctly positioned across the intended treatment site, tighten the hemostasis valve to maintain the catheter position.
7	Remove the source lumen plug. Withdraw the dummy ribbon proximal to the hemostasis valve and re-insert to verify the ability to access the treatment site.
8	Remove the dummy ribbon from the Checkmate Catheter and discard.
9	Visually check that there are no kinks in the proximal section of the Checkmate Catheter.
10	Ensure that an ACT taken just prior to the radiation dwell time is greater than 300 sec. (> 350 sec. If a Hematec analyzer is used).

Illustration

12.3.4 Intravascular Radiation Therapy Procedure

Warnings:

- Do not completely withdraw the source ribbon from the shielded delivery device. If this occurs, reinsert the source ribbon into the delivery device. Notify the institutional radiation safety officer immediately and follow the established radiation safety protocol.

Precautions:

- The Checkmate Delivery System and the transport cart are **NON-STERILE** and should remain outside of the sterile field.
- It is recommended that survey meter readings are recorded several times during the procedure to ensure that the radioactivity remains within an acceptable level.
- Maintain visual and audio contact with the patient during the intravascular brachytherapy procedure.
- Maintain hemodynamic monitoring of the patient during the intravascular brachytherapy procedure.
- If excessive resistance is encountered during the insertion, retract the source ribbon back into the Checkmate Delivery Device. Do not re-advance the radioactive source ribbon until the cause of resistance has been remedied, or a new Checkmate Catheter has been introduced.

- If significant symptoms of ischemia occur, the treatment may be fractionated. Rapidly retract the source ribbon into the Checkmate Delivery Device. Record the exposure time. Resolve the ischemic symptoms before re-introducing the source ribbon for the remaining treatment time. Fractionation of treatment time increases the radiation exposure to the radiation oncologist and to the patient. Use fractionation only if significant ischemia occurs.
- The proximal end and the source lumen of the catheter are no longer sterile after connection to the Checkmate Delivery Device. Handle per site procedures.

Step	Action
1	Transport the Checkmate Delivery System to a location within range of the patient but outside of the sterile field.
2	Remove the metal end caps from both ends of the shielded delivery device. Uncoil the ribbon from the spool (proximal end of the shielded delivery device).
3	Remove the threaded cap from the distal end of the shielded delivery device; replace it with a rotating luer connector. Connect the catheter hub to the rotating luer connector of the delivery device. NOTE: DO NOT rotate the catheter.
4	Transport the portable lead shield(s) to the side(s) of the patient to minimize radiation exposure to attending personnel. Position the shields as defined by institutional radiation safety procedures.
5	When ready to initiate the intravascular brachytherapy, all personnel should be positioned behind appropriate shielding as defined by institutional radiation safety procedures.
6	Open the fitting at the proximal end of the delivery device. The radiation oncologist rapidly advances the radioactive source ribbon through the Checkmate Catheter to the end of the source lumen. Verify the position of the source ribbon with the fluoroscope, utilizing the radiopaque markers and contrast injection. Secure the source ribbon in place.
7	Begin timing of the dwell time as soon as the radioactive source ribbon is positioned.
8	Monitor the patient closely during the treatment time with the Ir-192 source ribbon. NOTE: Verify the source location if the delivery device, cart or catheter are moved, or if the patient shifts position during the treatment time.
9	At the conclusion of the elapsed dwell time, the radiation oncologist releases the source ribbon and rapidly withdraws the source ribbon into the Checkmate Delivery Device. Use the visual markers on the source ribbon and a survey meter to ensure that the source ribbon is correctly positioned within the delivery device.
10	Secure the fully retracted source ribbon by tightening the fitting on the proximal end of the delivery device. Remove the luer connector and re-place the threaded cap over the exit port on the distal end of the delivery device. Appropriately licensed personnel performs a radiation survey to ensure that the source ribbon is properly contained within the Checkmate Delivery Device. Record the measurements.
11	Personnel may move from behind the radiation shielding. NOTE: Standard shielding practices for fluoroscopy must still be followed.
12	Disconnect the catheter from the Checkmate Delivery Device. NOTE: Placement of a new stent during the radiation procedure has been associated with a higher rate of late thrombosis in comparison to the placebo arm. Every attempt should be made to avoid new stent placement in the irradiated area. However, if placement of a new stent was necessary, it is recommended that the patient be placed on antiplatelet therapy.
13	Transport the Checkmate Delivery Device to a secure, restricted access area that has been designated for and meets the requirements for radioactive storage.

12.4 Withdrawal Procedure

Precautions

- DO NOT advance the catheter over the floppy portion of the guidewire as the guidewire may prolapse on withdrawal of the catheter. If this occurs, attempt to resolve the prolapse by gently pulling back on the guidewire while simultaneously advancing the catheter. If the prolapse persists, disengage the catheter from the guidewire by continuing to advance the catheter while gently pulling back on the guidewire. Remove the catheter (or remove the catheter and guidewire as a unit).

- If the radioactivity readings register above the acceptable limits, notify the institutional safety officer immediately and follow the established institutional radiation safety protocol.

Step	Action
1	Remove and discard the Checkmate Catheter.
2	Use a survey meter to survey the patient and the catheter for any radiation. Record the measurements.
3	Perform a post procedure angiogram if required.
4	Remove the guidewire, guiding catheter and the sheath introducer from the vasculature per standard techniques.
5	Close the arterial opening per desired technique.

12.5 Emergency Ir-192 Source Ribbon Removal

Precautions

- This procedure should only be performed by, or under the direction of, appropriately trained personnel.

Step	Action
1	Disconnect the Checkmate Catheter from the delivery device.
2	Withdraw the Ir-192 source ribbon manually from the patient and immediately deposit the radioactive portion of the Ir-192 source ribbon in a shielded emergency container. NOTE: Ensure that the emergency container provides appropriate shielding.
3	Appropriately licensed personnel perform a radiation survey of the patient and general vicinity to ensure that the radioactive portion of the Ir-192 source ribbon is completely deposited in the shielded emergency container.
4	Cut off the ribbon proximal of the shielded emergency container. Follow site specific requirements for handling of the shielded emergency container.
5	The Checkmate Delivery System and all parts of the Ir-192 source ribbon need to be returned to Best Industries (Springfield, VA, USA). Refer to the Return Shipping Guidelines.
6	Contact Cordis at (800) 327-7714 or (732) 562-3097.
7	Follow site specific requirements for documentation of this emergency procedure

12.6 Emergency Checkmate Catheter/Ir-192 Source Ribbon Removal

In the event of a (suspected) ribbon fracture, determined visually or by high radiation survey readings following the withdrawal of the Ir-192 source ribbon, the Checkmate Catheter and Ir-192 source ribbon should be removed as one unit.

For detailed instructions on removal of the Checkmate Catheter, see the Checkmate Catheter Instructions for Use.

Precautions

- This procedure should only be performed by, or under the direction of, appropriately trained personnel.

Step	Action
After removal of the Checkmate Catheter and the Ir-192 source ribbon, follow this procedure:	
1	Using wire cutters, cut off the distal section of the catheter which contains the radioactive seed train and deposit this in an emergency container. NOTE: Ensure that the emergency container provides appropriate shielding.
2	Appropriately licensed personnel perform a radiation survey of the patient and general vicinity to ensure that the radioactive portion of the Ir-192 source ribbon is completely deposited in the shielded emergency container.
3	Follow site specific requirements for handling of the shielded emergency container.
4	The Checkmate Delivery System and all parts of the Ir-192 source ribbon need to be returned to Best Industries (Springfield, VA, USA). Refer to the Return Shipping Guidelines.
5	Contact Cordis at (800) 327-7714 or (732) 562-3097.
6	Follow site specific requirements for documentation of this emergency procedure

12.7 Return Shipping Guidelines

Step	Action
1	Refer to the return shipping guidelines supplied with the Checkmate Delivery System (in the Return Shipping Package) for the return procedure. The Checkmate Delivery Device and Ir-192 source ribbon need to be returned to Best Industries (Springfield, VA, USA), phone (703) 451-2378, fax (703) 451-4977.

13 References

P. Teirstein, V. Massullo, S. Jani, et al., "Catheter-Based Radiation Therapy to Inhibit Restenosis after Coronary Stenting", NEJM, v. 336, n. 24, pp. 1697-1703.

Date of Labeling Modification: November 2000.

14 Disclaimer

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15 Revision History

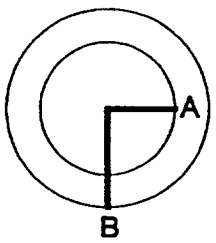
Date	Rev	
June 1999	1	First revision of final draft labeling.
February 2000	2	FDA requested modifications
May 2000	3	Change name from IRT to Checkmate Update clinical results
	4	Change Table 7.1 to Peto results Modify radiation worksheet Add chart from Rosanna Chan Add air kerma strength conversion factor Update Indications for Use, Contraindications & Warnings per recommendation of the FDA Panel.
July 2000	5	Update per meeting with FDA
October 2000	6	Updated in response to deficiency question
November 2000	7	Update per FDA request

Attachment 1: RADIATION THERAPY WORKSHEET

Dosimetry calculation

Target Vessel: Take measurements using IVUS at a minimum of three (3) sites along the stented vessel segment to determine the shortest and longest distance between the midpoint of the catheter and the leading edge of the media.

A = _____ mm (shortest distance)
B = _____ mm (longest distance)



Dose Prescription:

Ribbon: ____ Seeds
Dose: _____cGy at ____ mm distance

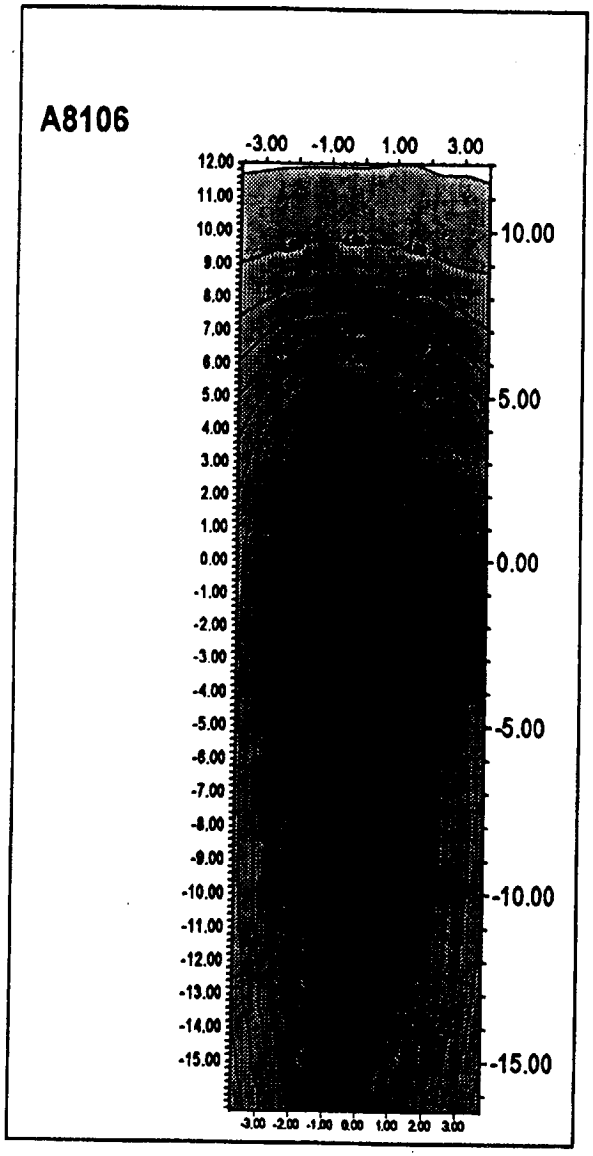
Dose Calculation:
D_A = _____cGy
D_B = _____cGy
Total Activity = _____ mCi on __/__/__ (date)
Activity per seed = _____ mCi

Distance (mm)	Dose Rate (cGy/min) for 1 mCi per seed			TX Time (min) = Prescribed Dose (cGy) / (Activity per seed (mCi) x Dose Rate (cGy/min) at the prescribed distance (see adjacent Table))
	6 Seeds*	10 Seeds*	14 Seeds*	
0.9	7.04	7.13	7.16	
1.0	6.22	6.31	6.34	
1.1	5.55	5.64	5.67	
1.2	5.01	5.09	5.12	
1.3	4.55	4.64	4.66	
1.4	4.16	4.25	4.26	
1.5	3.83	3.92	3.93	
1.6	3.55	3.64	3.65	
1.7	3.30	3.39	3.40	
1.8	3.08	3.17	3.18	
1.9	2.89	2.98	2.99	
2.0	2.72	2.81	2.82	
2.1	2.57	2.65	2.66	
2.2	2.43	2.51	2.54	
2.3	2.30	2.39	2.41	
2.4	2.19	2.28	2.30	
2.5	2.08	2.17	2.20	
2.6	1.99	2.08	2.11	
2.7	1.91	1.99	2.02	
2.8	1.82	1.92	1.94	
2.9	1.74	1.84	1.87	
3.0	1.68	1.77	1.80	
3.1	1.61	1.71	1.74	
3.2	1.55	1.65	1.68	
3.3	1.49	1.59	1.63	
3.4	1.44	1.54	1.57	
3.5	1.39	1.49	1.53	
3.6	1.34	1.44	1.47	
3.8	1.25	1.35	1.39	
4.0	1.18	1.27	1.31	
4.2	1.12	1.21	1.26	
4.4	1.06	1.15	1.19	

* At distances less than 2.1 mm from the source ribbon the maximum dose rate at the perpendicular bisector of a central seed is listed. At distances greater than 2.1 mm from the source ribbon the average dose rate over two central seeds and the space between them is listed.

Treatment Time: _____ minutes _____ seconds.

Attachment 2: Isodose Distribution for 6-seed Ir-192 Source Ribbon at Depth of 2.06mm from Source Center



A8106 (depth of 2.06mm)
Ir-192 ribbon
Surface view of isodose lines